CARLO TORTI

UNIT OF INFECTIOUS DISEASES
UNIVERSITY "MAGNA GRAECIA" , CATANZARO, ITALY

INSTITUTE OF INFECTIOUS AND TROPICAL DISEASES, UNIVERSITY OF BRESCIA, ITALY

Randomized and controlled studies, blind and double-blind studies, non inferiority and superiority studies, BE and BA studies. Peculiarities of developing settings.

MWANZA, JUNE 11, 2012

Acknowledgements and thanks

Many of the following slides were presented by Linda Wittkop, MD, PhD

Inserm U897 Centre of Epidemiology and Biostatistics

ISPED Bordeaux School of Public Health

University Bordeaux Segalen, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France

at the first Summer School on Infectious Diseases, University of Brescia, Italy (supported by NEAT)

How is evidence rated?

Infectious Diseases Society of America-US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥1 properly randomized, controlled trial
II	Evidence from ≥1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. From [11].

Khan A R et al. Clin Infect Dis. 2010;51:1147-1156

Hierarchy of Epidemiologic Study Design

Case reports

Case series

Ecologic studies

Cross-sectional studies

Cohort studies

Randomized controlled trials

Generate hypotheses

Establish causality

What is the best design?

Table 1 Comparison of cohort studies and randomised controlled trials

Item	Cohort studies	Randomised controlled trials
Populations studied	Diverse populations of patients who are observed in a range of settings	Highly selected populations recruited on the basis of detailed criteria and treated at selected sites
Allocation to the intervention	Based on decisions made by providers or patients	Based on chance and controlled by investigators
Outcomes	Can be defined after the intervention and can include rare or unexpected events	Primary outcomes are determined before patients are entered into study and are focused on predicted benefits and risks
Follow-up	Many cohort studies rely on existing experience (retrospective studies) and can provide an opportunity for long follow-up	Prospective studies; often have short follow-up because of costs and pressure to produce timely evidence
Analysis	Sophisticated multivariate techniques may be required to deal with confounding	Analysis is straightforward

BMJ VOLUME 330 16 APRIL 2005

Case series < case-control < observ. cohort < randomized

Generate hypotheses

Establish causality

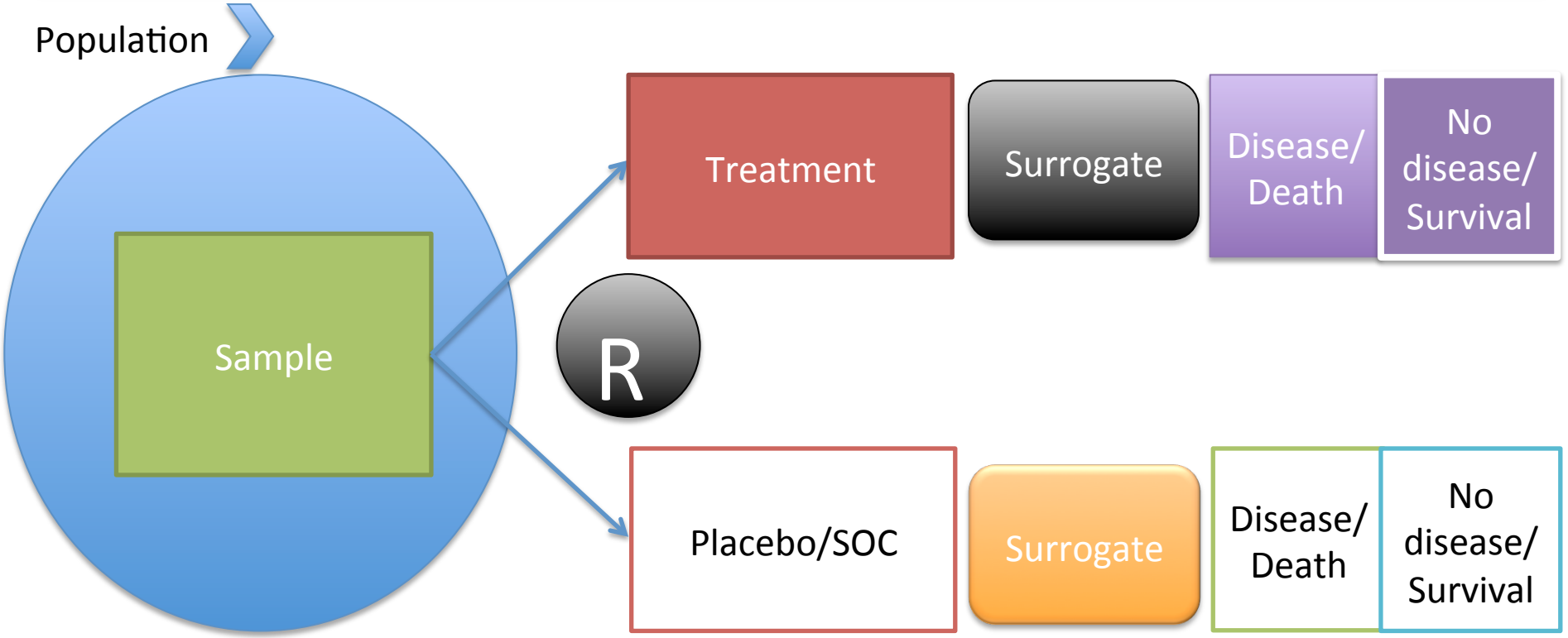
What was randomisation important for?

- We want the treatment and comparison groups to be comparable in all respects except the one being studied
- to ensure as much as possible that the distribution of all factors and population characteristics, except for the therapy being studied, is based on chance and not to some other factor such as patient or investigator preference (bias)
- will provide comparable groups for most factors so that differences in outcomes at the end of the trial can be attributed to the intervention being tested

Randomised controlled clinical trials

- Patients are randomly assigned to 2 or more treatment groups
- Experimental group receives 'new' intervention
- Comparison group receives standard of care or placebo
- Well balanced for confounders
- Allows direct assessment of treatment intervention

RCT: enrollment, randomization and outcome



In a randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions, (e) measures outcome variables during follow-up

The purpose of a control group

- To allow descrimination of patient outcomes (ex: virological failure) caused by the test treatment from outcomes caused by other factors
- Tell us what would have happened to patients
  - if they had not received the test treatment or
  - if they had received a different treatment known to be effective

Blinding

Figure 2: **The authors blinded and masked**

Epidemiology series

Blinding in randomised trials: hiding who got what

Kenneth F Schulz, David A Grimes

reporting of clinical trials). We prefer blinding because it has a long history, maintains worldwide recognition, creates strong imagery, and permeates the ICH guidelines.[3]

- Objective: to keep the comparability between the groups

Superiority trial

- Is designed to detect a difference between the two treatment arms
- Definition of a primary endpoint :
  - % of patients with a VL <50 cp/mL at 24 weeks
- Definition of the difference you want to show between the two treatment arms
  - In Lazzarin et al (simplified):
    - Virological success for TMC125 group: 55%
    - Virological success for the Placebo group: 35%
    - → difference = 20%
  - needed to calculate the samples size

Estimation with confidence intervals in a superiority trial

It is not statistically significant!

Because the CI includes the d=0 value

d < 0
Negative effect

d = 0
No difference

d > 0
Positive effect

Equivalence/Non-inferiority trials

- Equivalence trials
  - Aim to determine whether one intervention is therapeutically similar to another

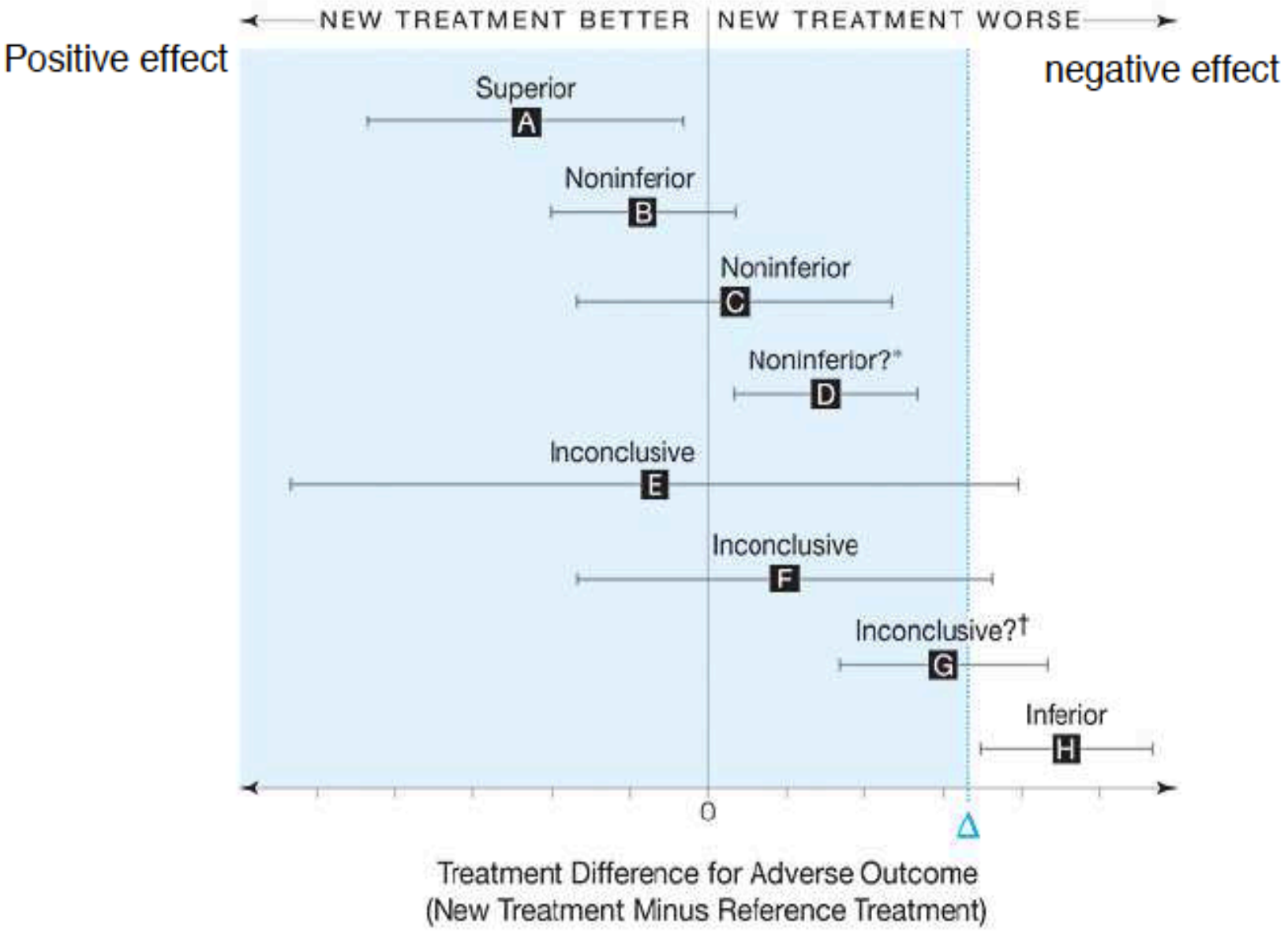
- Non-inferiority trial
  - seeks to determine whether a new treatment is no worse than a reference treatment

Piaggio JAMA 2006 JAMA. 2006 Mar 8;295(10):1152-60.

But remember

- Not all innovations can easily be compared to a placebo
- Innovations can be interesting even without being more efficient :
  - tolerance, costs, pill burden
- Gallant *et al.*
  - The regimen of TDF, FTC, EFV was to be considered not inferior to the regimen of ZID, 3TC, and EFV if the lower bound of the 95% CI for the difference between the two groups, for the primary end point (in the proportion of patients with an HIV RNA level of less than 400 copies/mL) was no lower than –13%.

Figure. Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials Error bars indicate 2-sided 95% confidence intervals (CIs).



Piaggio, G. et al. JAMA 2006;295:1152-1160

Peculiarities in resource limited settings

- We need to test drugs in different populations (e.g., genetics) … but the final objective is to provide this population with drugs!
- We need to administer the informed consent in a compatible manner
- We need resources, e.g.:
  - Central randomization for an easy and true blinding
  - Intensity and lenght of follow-up (reduce loss to follow-up rates)

Facts

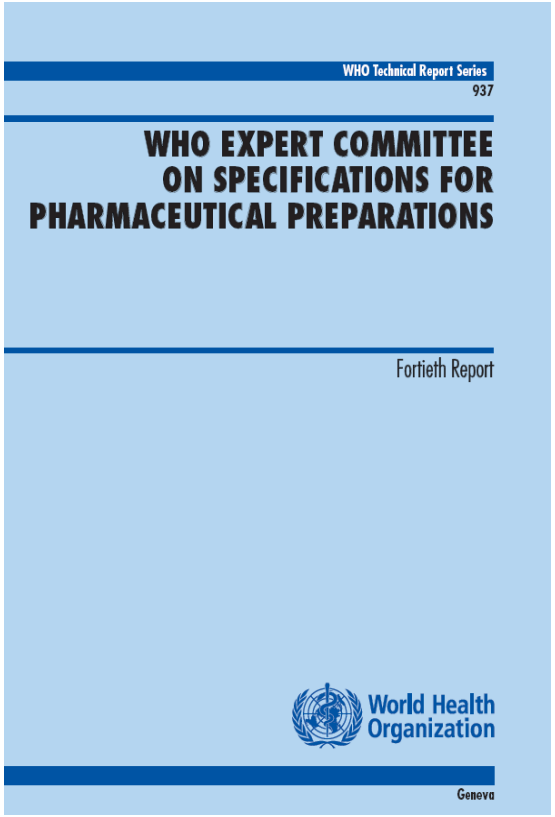
- Generic drugs are safe and effective alternatives to brand name prescriptions
- Generic drugs can help both consumers and the government reduce the cost of prescription drugs

Why do we need Bioequivalence studies?

- No clinical studies have been performed in patients with the Generic Product to support its Efficacy and Safety.
- With data to support similar in vivo performance (= Bioequivalence)
  Efficacy and Safety
  data can be extrapolated from the Innovator Product to the Generic Product.

WHO Guidelines

- Annex 7 of WHO Technical Report Series, No. 937, 2006
- Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

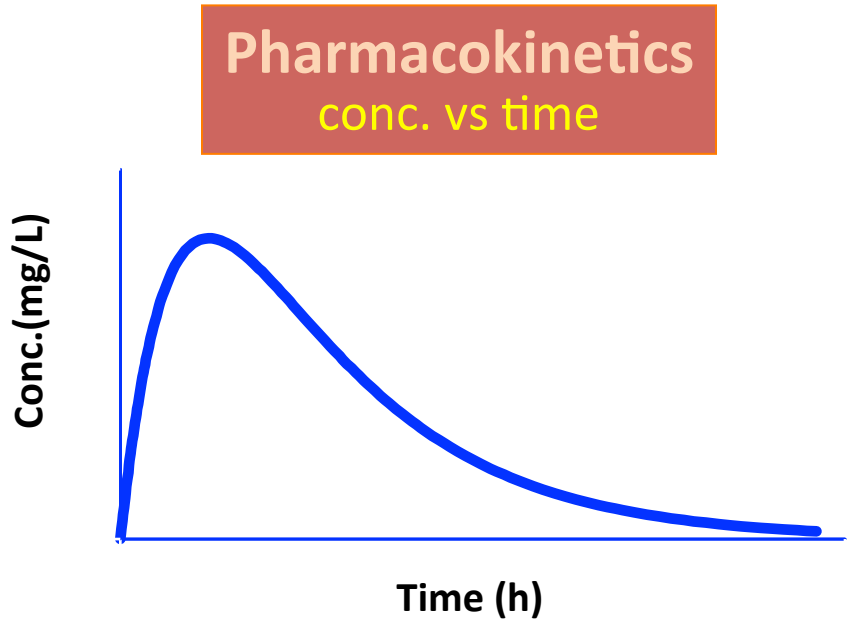


Additional Guidance

- Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate release, solid oral dosage forms (Annex 8)
- Additional guidance for organizations performing in vivo bioequivalence studies (Annex 9)
- Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products (Annex 11)

Bioavailability

- The extent and rate at which its active moiety is delivered from pharmaceutical form and becomes available in the systemic circulation



Scheme of Oral Dosage Form

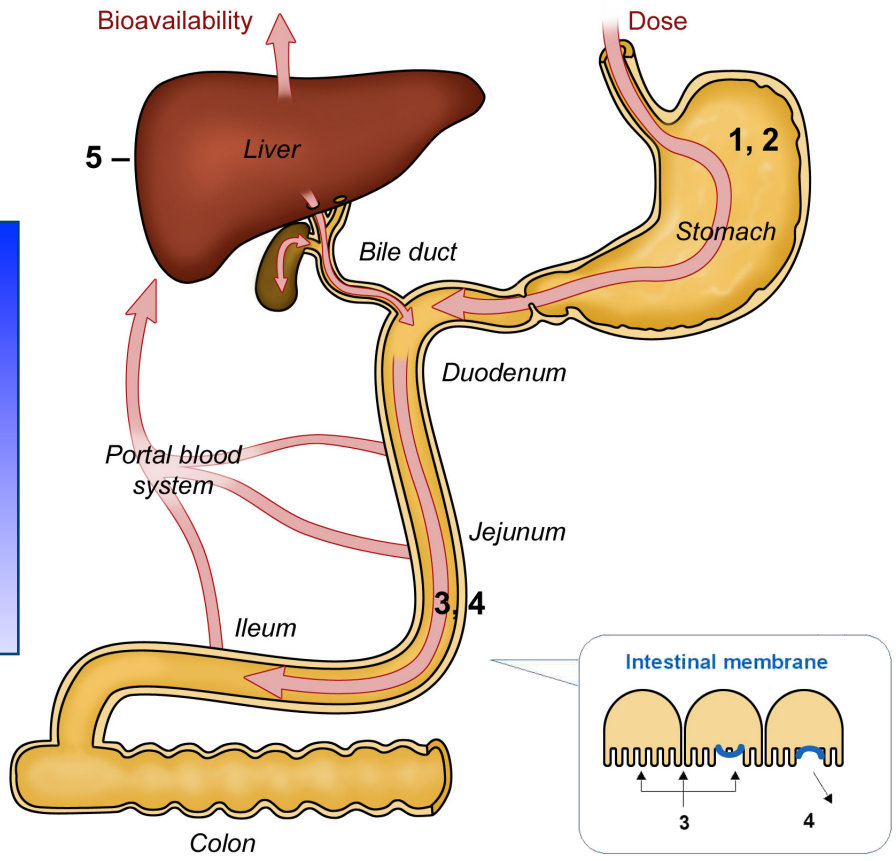
Human Intestinal Absorption (*HIA*)

1,2 – Stability + Solubility

3 – Passive + Active Tr.

4 – Pgp efflux + CYP 3A4

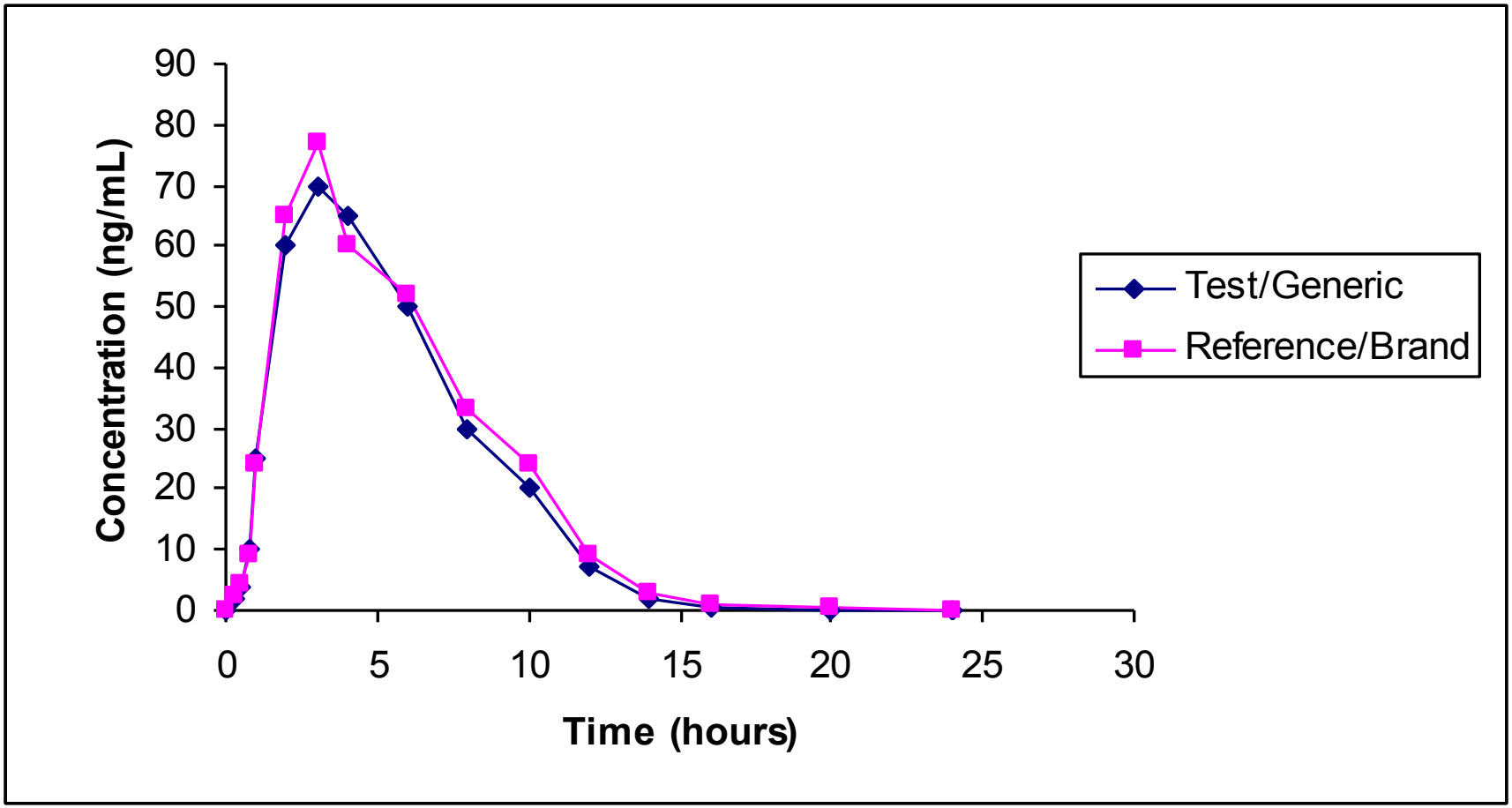
Oral Bioavailability (%*F*)



Bioequivalence (BE): Definition

"the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

Bioequivalence

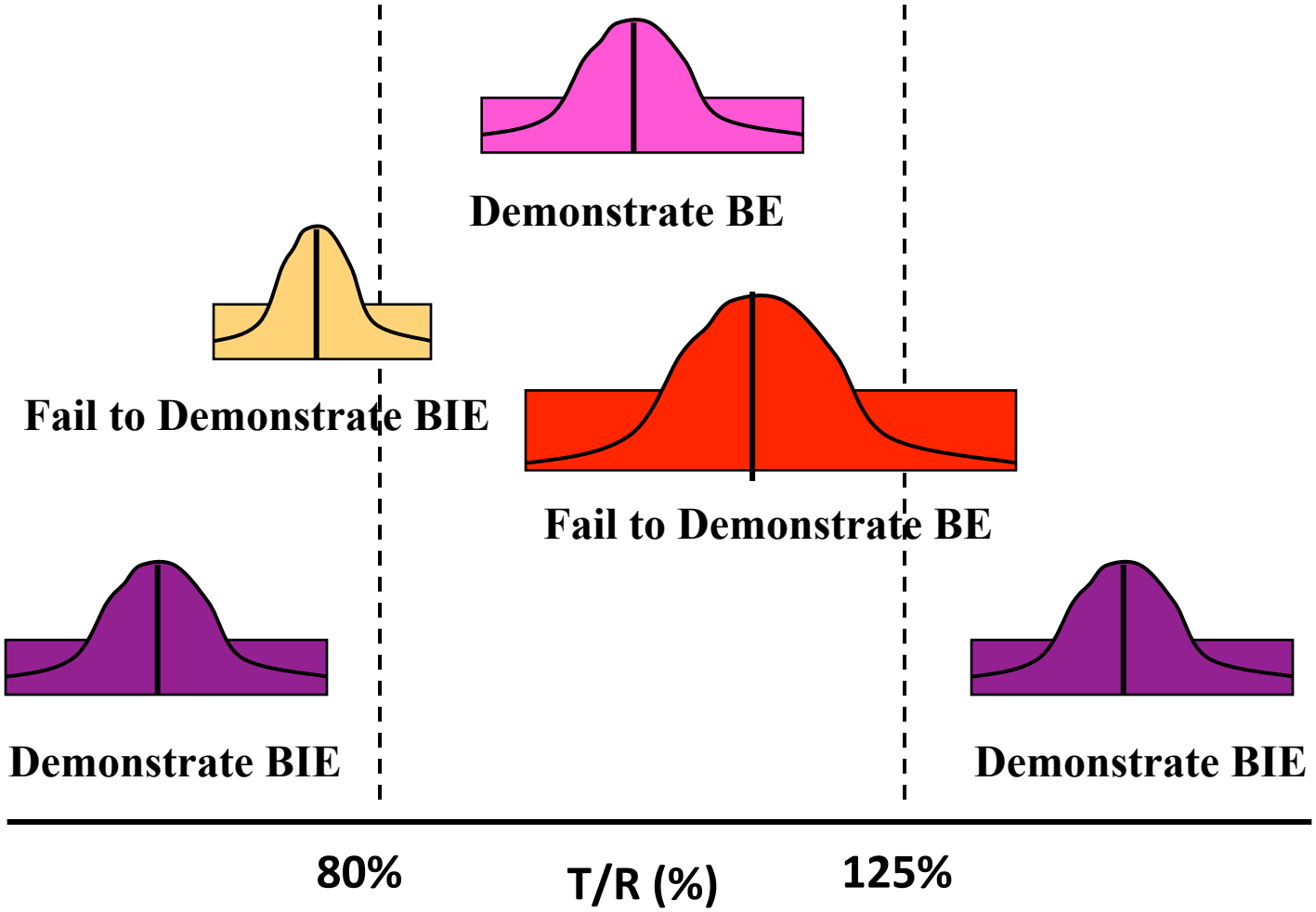


Statistical Analysis
(Two one-sided Tests Procedure)

- AUC (Extent) and C_{max} (Rate) – Log transformation

- 90% Confidence Intervals (CI) of the difference in Log (AUC_t) –Log (AUC_R) must fit between 80%-125%

BE Results (90% CI)



Study Designs

- Single-dose, two-way crossover, fasted
- Single-dose, two-way crossover, fed

Alternative

- Single-dose, parallel, fasted (Long half-life)
- Single-dose, replicate design (Highly Variable Drugs)
- Multiple-dose, two-way crossover, fasted (Less Sensitive, non-linear kinetic)

Parallel or crossover?, Fasted or Fed?, Single or Multiple?, Replicate or nonreplicate?

Study Designs

- Duration of washout period for cross-over design
- should be approximately > 5 times the plasma apparent terminal half-life
- However, should be adjusted accordingly for drugs with complex kinetic model

Study Designs

- Sample size determination
- significant level ($\alpha = 0.05$)
- 20% deviation from the reference product
- power > 80%

- Sample time determination
- adequate data points around t_{max}
- 3 or more time of $t_{1/2}$ to around $AUC_{0\text{-}t}$ = at least 80% $AUC_{0\text{-}inf}$

Peculiarities in resource limited settings

- We need to test generic drugs esp. in these settings
- Caution for variability in PK/PD characteristics:
  - Genetically diverse populations
  - Environmentally diverse populations
- Validity of the results (technical)

Strategies to improve International Collaborative research

- Scientists in RLS:
  - Choose collaborators carefully
  - Learn English or other langages of the collaborators
  - Become familiar with the international scientific literature
  - Be sure that collaboration will build local research capacity
  - Clarify administrative and scientific expectation in advance
- Scientists in the IC's
  - Choose collaborators carefully
  - Learn the local langage and culture
  - Be sensitive to local ethical issues
  - Encourage local collaboration in all aspects of the research process
  - Clarify administrative and scientific expectation in advance

FUNDING AGENCIES