Investigator Responsibilities in Protecting Participants in the Conduct of Bioequivalence Studies

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Topics for Discussion

Introduction

- Definitions/Purpose of Bioequivalence studies
- Design of Bioequivalence Studies
- Difference from other Clinical Studies

Investigator responsibilities

patient selection

informed consent

conduct of studies

adverse events

compensation

References

- ASEAN GUIDELINES FOR THE CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES. *FINAL DRAFT : 21 JULY 2004*
- **Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability.** WHO Technical Report Series, No. 937, 2006
- **Annex 9: additional guidance for organizations performing in vivo bioequivalence studies. World Health Organization** Technical Report Series, 2006
- Rani S. Bioequivalence: Issues and Perspectives. Indian J Pharmacol. 2007 (39): 218-225.
- **Remuneration for Research Subjects** , The Partners Human Research Committee (PHRC) posted at http://healthcare.partners.org/phsirb/remun.htm
- **www.fda.gov/cder/ogd**

Drug Quality

- must be proven by pharmaceutical companies for all products
- Generic/ me-too drugs should also prove they are of good quality

- SUBSTANDARD DRUGS ARE A GLOBAL PROBLEM

- Regulatory authorities must ensure standards of quality, efficacy, and safety of registered drugs

FDA requirements for generic drugs (www.fda.gov/cder/ogd)

- Generic drugs must:
  1. contain the same active ingredients as the innovator drugs as the innovator drug
  2. be identical in strength, dosage form, and route of administration
  3. have the same use indications
  4. meet the same batch requirements for identity , strength, purity and quality
  5. be manufactured under the same strict standards of GMP required for innovator products.
  6. be bio-equivalent

Bioequivalence testing

Bioavailability

refers to the relative amount of drug from an administered dosage form which enters the systemic circulation and the rate at which the drug appears in the systemic circulation

Bioequivalence testing

Compares the bioavailability of the active ingredient present in a given drug vs. a previously tested comparator drug with established bioavailability characteristics

Bioequivalence testing

- A BE study is a type of clinical study conducted to compare two medicinal products containing the same amount of the same active ingredient(s), in the same dosage form that meet the same or comparable standards but produced by different pharmaceutical companies.
- This clinical study examines scientifically if the two medicinal products will give rise to the same blood-level concentrations in a human subject at specific interval after consuming orally the two different products.

BIOEQUIVALENCE OF A DRUG PRODUCT

- It is achieved if its extent and rate of absorption are not statistically significantly different from those of the reference product when administered at the same molar dose

METHODOLOGY OF BIOEQUIVALENCE STUDIES

DESIGN:

single dose study

two period, two sequence cross-over design

STUDY POPULATION

24 healthy subjects

– Standard requirement for BE studies:

- Canada :12
- US :24 – 36
- WHO :12

Methodology

- **At Study Period 1:** All volunteers will stay for one or more days in the study wards. The volunteers will take one dose of the medicinal product (either Brand A or Brand B) and allow the clinical research team to collect their blood samples at specific time intervals. Doses are administered under close supervision and in a randomised method. After this is completed, the subjects will return home.

- **At Study Period 2:** After a period of wash-out determined by the principal investigator, the volunteers will check into the study ward to repeat the same procedures as in Study Period 1 but with a different Brand product (which they did not take during the first study period). The blood samples collection will be repeated at the same specific time intervals.

- After the completion of the clinical phase, all the collected blood samples from Study period 1 and 2 will be sent to a pharmacokinetics laboratory to conduct the concentration analysis phase. This analytical phase will determine whether the two medicinal products are Bioequivalent or not.

METHODOLOGY OF BIOEQUIVALENCE STUDIES

- Sampling time
  - Blood samples are taken at a frequency sufficient for assessing Cmax, AUC and other parameters.
  - Sampling points include a pre-dose sample, at least 1–2 points before Cmax, 2 points around Cmax and 3–4 points during the elimination phase.

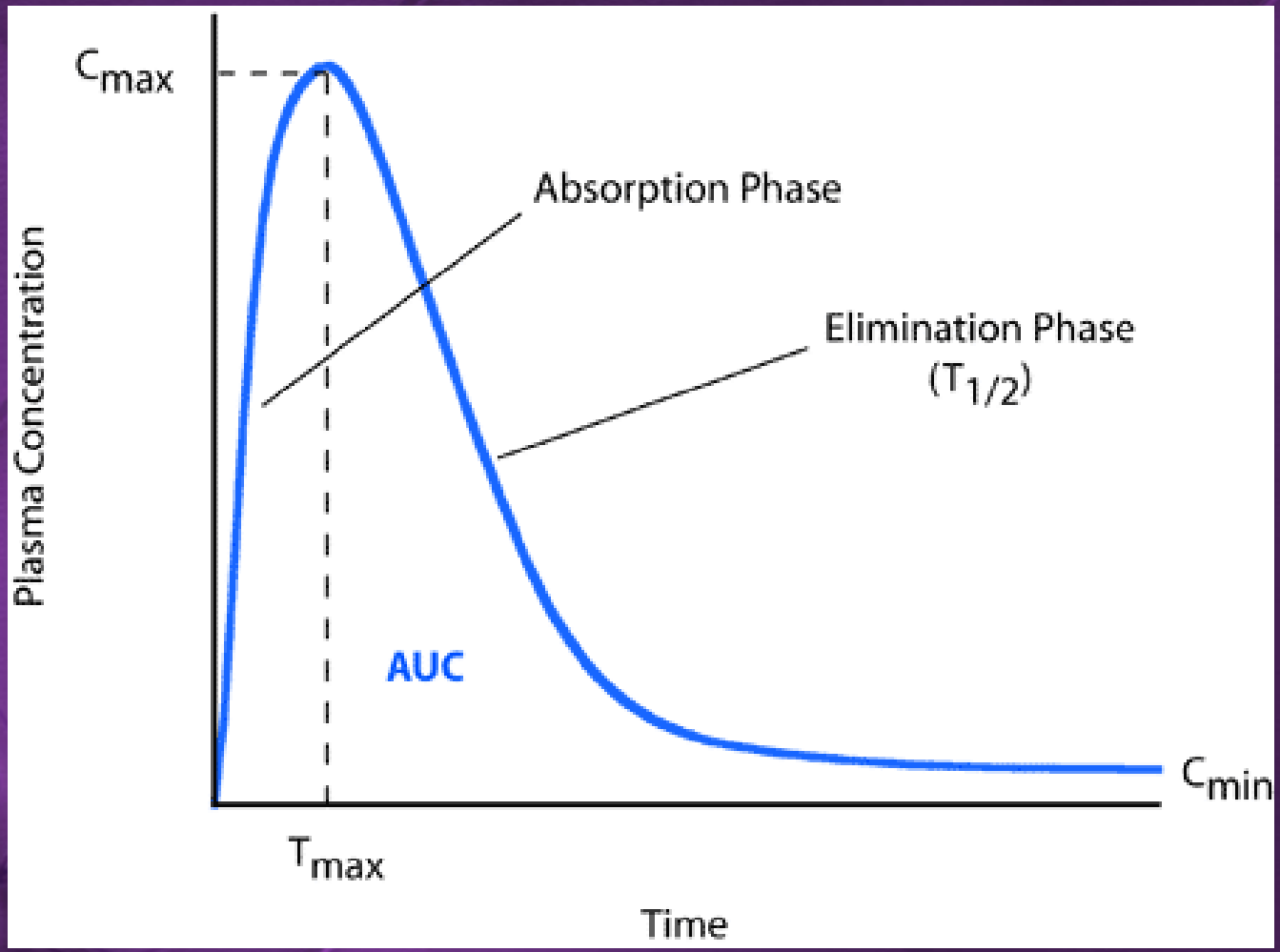
US FDA protocol: 12 to 18 samples, including a pre dose sample collected per subject per dose

Study standardization

- The magnitude of variability other than in the pharmaceutical products is minimized

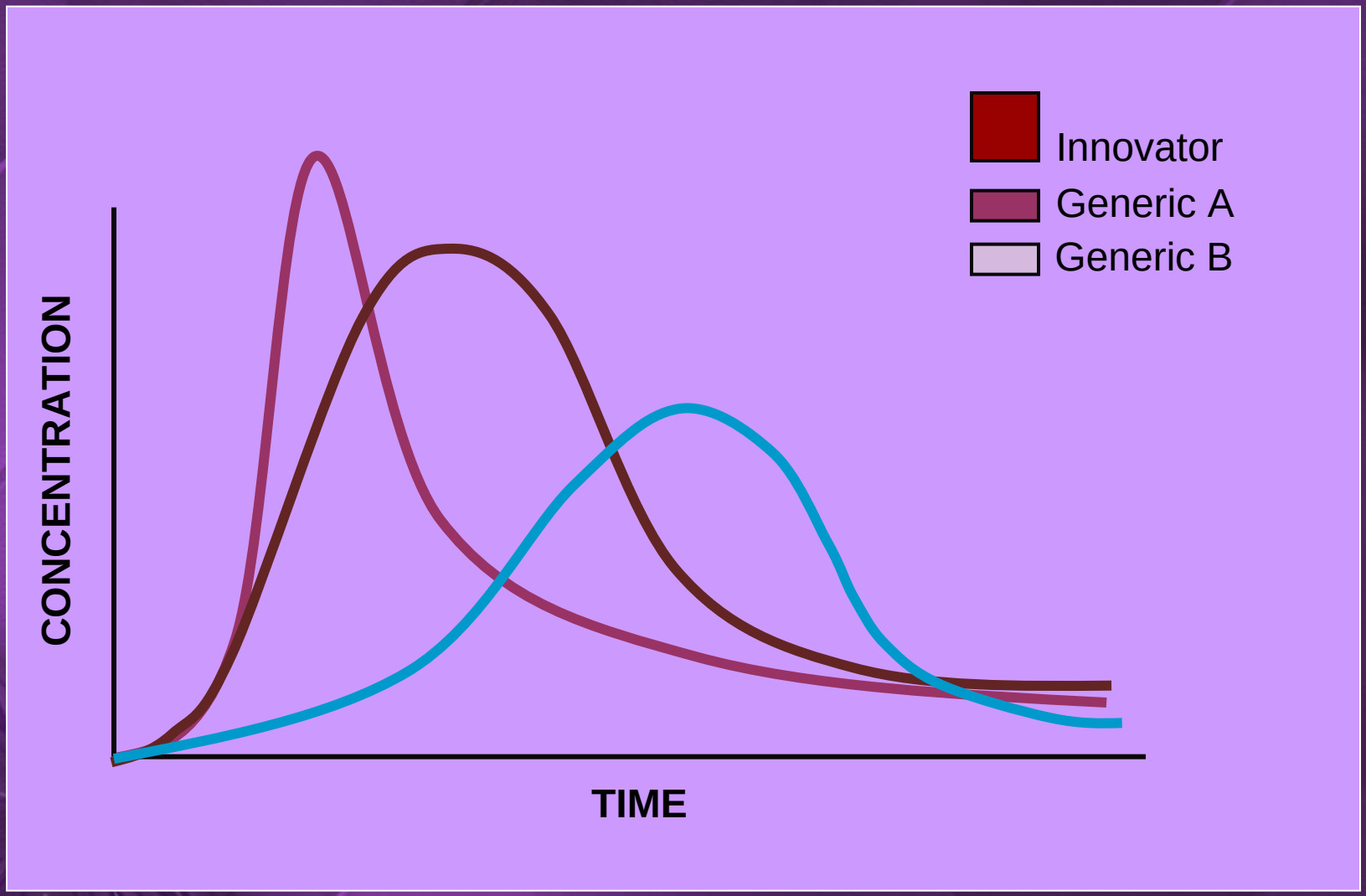
  - Exercise/activities
  - Diet/ fluid intake/ restriction of the intake of alcohol, caffeine, certain fruit juices and concomitant medicines
  - posture

Pharmacokinetic parameters



AUC = Area under the concentration–time curve
Cmax = Maximum plasma concentration

Bioequivalence in Clinical Practice



Special Features of Bioequivalence Studies

1. Healthy volunteers-

   -homogenous groups to avoid

   inter-subject variability, minimizes the chances of bioequivalence due to changes in the disease process over time rather than differences in formulations

2. Non-therapeutic trial- still considered a clinical trial; must abide by guidelines of a clinical trial

3. Proving quality/equivalence of generic/me-too drug

Investigators

should have appropriate qualifications, be suitably trained and have experience in the conduct of bioequivalence studies (the legal status of persons authorized to act as investigators differs between countries), and at least one investigator must be legally allowed to practice medicine.

The medically qualified investigator should be responsible for the integrity, health and welfare of the subjects during the trial, and the accurate documentation of all trial-related clinical data.

Investigator responsibilities for the protection of BE Study subjects

- patient selection
- informed consent
- conduct of studies
- adverse events
- compensation

Volunteers/subjects

- Note: the organization or institution performing bioequivalence studies should ideally have a pool of healthy volunteers who have been medically tested and selected in advance.
- Recruitment of volunteers undertaken immediately before the study is often done in a hurry and may compromise adherence to the selection criteria, especially for safety.

Patient selection- screening

- thorough medical history
- physical examination
- The ff. laboratory tests are performed:
  - Complete blood count
  - Erythrocyte sedimentation rate
  - fasting blood glucose
  - blood urea nitrogen, creatinine
  - AST, ALT, alkaline phosphatase, total protein, albumin, and globulin
  - Assay for hepatitis B (HBs) antigen
  - Chest radiography
  - Electrocardiography
  - Urinalysis

Volunteers are included into the study if they satisfied all of the following criteria:

- Healthy male subjects between 18 to 45 years old weighing at least 50 kilos
- With normal laboratory values
- Able to provide an informed consent independently

Exclusion criteria

- Recent or chronic smoking history
- Recent or chronic alcoholic beverage intake
- Recent or past history of drug abuse
- Current or recent (i.e., preceding 2 weeks) use of any other systemic drug or medication
- Any history of recent or chronic illnesses, such as
    - Viral hepatitis
    - Any form or severity of recent or chronic liver disease
    - Any form or severity of recent or chronic kidney disease
    - Anemia from any cause
    - Any cardiac disease
    - Presence of recent infection
    - Dyslipidemia
    - Allergy
    - Diabetes mellitus
- Allergy to the drugs which will be administered
- Inability to give an independent informed consent

Investigator responsibility

for patient selection

- MUST ENSURE PATIENT IS HEALTHY AND FIT TO BE INCLUDED IN THE BIOEQUIVALENCE STUDY

- If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to use patients instead, under suitable precautions and supervision.

Informed consent

- Informed consent of potential subjects should be obtained for any screening procedures required to determine eligibility for the study, in addition to informed consent for participation in the research portion of the study.
- Objectives clearly stated
- Aware of study drug, uses of the drug, possible adverse effects
- Clear to subjects that they have no direct benefit
- Consumers of the drug will be the ones to benefit
- Clear statements about procedures
- Clear statements about time needed for the study
- Volunteers- no coercion

Conduct of the study

- sufficient space to accommodate the study subjects.
- for beds and facilities for overnight stays
- Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users
- provide non-strenuous activities- watching TV, reading magazines, listening to music

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Monitoring of Volunteers/Adverse events

- must be carried out under conditions which ensure adequate safety for the subjects.
- monitored for onset of side-effects, toxicity, or any intercurrent disease may be recorded, and appropriate measures taken.

  Regular taking of vital signs

  physicians present during the entire study
- availability of emergency or first-aid equipment and appropriate rescue medication for use in emergencies.
- adequate facilities for the proper care of subjects who require emergency or other medical care

Adverse events

- The investigator(s) should be responsible for medical decisions in case of adverse events and for notifying the relevant health authorities, the sponsor and, when applicable, the ethics committee, without delay.

In the case of serious adverse events, appropriate timelines for reporting them should be respected as governed by national regulations.

Compensation

- Research subjects may be compensated for the time and effort they devote to clinical studies.
- compensation is pro-rated according to the amount of time devoted to the project
- healthy volunteers who will derive no medical benefit from their participation should be compensated **reasonably** for the time they devote to research projects.
- stipends paid to research subjects should provide fair compensation without undue pressure (coercion) to participate.
- Excessive monetary compensation may cause subjects to undertake risks or discomforts that they otherwise would not assume.

INVESTIGATORS DUTY

- Health and safety of the subjects is of foremost importance in the conduct of bioequivalence studies


THANK YOU!