Bioequivalence studies, design and evaluation of bioequivalence studies

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Introduction to Bioequivalence

- Bioequivalence studies are drug product performance tests that compare the bioavailability of the same active pharmaceutical ingredient from one drug product (test) to a second drug product (reference). Bioavailability and bioequivalence can be considered as measures of the drug product performance in vivo.

Need of Bioequivalence

- During drug development, bioequivalence studies are used to compare,

  (a) early and late clinical trial formulations;

  (b) formulations used in clinical trials and stability studies, if different;

  (c) clinical trial formulations and to-be-marketed drug products, if different; and

  (d) product strength equivalence, as appropriate.

- Bioequivalence study designs are used to support new formulations of previously approved products, such as a new fixed-dose combination version of two products approved for coadministration, or modified-release versions of immediate-release products.
- Bioequivalence studies may be needed to support regulatory approval of major changes in formulation, manufacturing, or site, in comparison to reference formulation.

Design of Bioequivalence

- The main objective for a bioequivalence study is that the drug bioavailability from test and reference products is not statistically different when administered to patients or subjects at the same molar dose from pharmaceutically equivalent drug products through the same route of administration under similar experimental conditions.
- The basic design for a bioequivalence study is determined by

(1) the scientific questions and objectives to be answered,

(2) the nature of the reference material and the dosage form to be tested,

(3) the availability of analytical methods,

(4) the pharmacokinetics and pharmacodynamics of the drug substance,

(5) the route of drug administration, and

(6) benefit–risk and ethical considerations with regard to testing in humans.

Bioequivalence study protocol

- **I. Title**

  A. Principal investigator (study director).

  B. Project/protocol number and date
- **I. Study objective**
- **III. Study design**

  A. Design

  B. Drug products

  1. Test product(s)

  2. Reference product

  C. Dosage regimen

  D. Sample collection schedule

  E. Housing/confinement

  F. Fasting/meals schedule

  G. Analytical methods

- **IV. Study population**
  - A. Subjects
  - B. Subject selection
    1. Medical history
    2. Physical examination
    3. Laboratory tests
  - C. Inclusion/exclusion criteria
    1. Inclusion criteria
    2. Exclusion criteria
  - D. Restrictions/prohibitions
- **V. Clinical procedures**
  - A. Dosage and drug administration
  - B. Biological sampling schedule and handling procedures
  - C. Activity of subjects
- **VI. Ethical considerations**
  - A. Basic principles
  - B. Institutional review board
  - C. Informed consent
  - D. Indications for subject withdrawal
  - E. Adverse reactions and emergency procedures
- **VII. Facilities**
- **VIII. Data analysis**
  - A. Analytical validation procedure
  - B. Statistical treatment of data
- **IX. Drug accountability**
- **X. Appendix**

Study design

- The FDA provides the guidance for the performance of: In vitro dissolution and In vivo bioequivalence studies which include(solid oral dosage form)
  1. Fasting study
  2. Food intervention study
  3. Sprinkle BE study (extended release capsules having beads)

Fasting studies

1. This study is required for all immediate release and modified release oral dosage forms.
2. Both male and female subjects are included.
3. Overnight fasting is required(at least 10 hrs).
4. After administration of drug fasting continued up to 4 more hrs.
5. Blood sampling is performed before dose and at different intervals after dose.
6. Plasma drug concentration-time profile is obtained.
7. No other medication given at least 1 week prior to study.
8. In some cases, a parallel design may be more appropriate for certain drug products, containing a drug with a very long elimination half-life.
9. A replicate design may be used for a drug product containing a drug that has high intrasubject variability.

Food intervention study

1. It uses single dose, randomized, 2 treatment, 2 period crossover study.
2. Conducted using meal conditions that have greatest effect on GI physiology.
3. Meal containing high calories(50% of total caloric content) and fat (800-1000 cal) is taken.
4. After a overnight fast of 10 hrs, meal is given 30min prior to dosing.
5. The meal is consumed over 30min with administration of drug(with 240ml of water) immediately after meal.
6. No food is allowed 4hrs after dosing.
7. Study on drugs like ibuprofen and naproxen which is affected by food.

EVALUATION OF bioequivalence studies

Analytical Method:-

- Must be validated for accuracy, precision, sensitivity,& specificity.
- Using more than one analytical method for a study is not valid—different methods may yield different results.
- Data presented in both tabulated and graphic form for evaluation.
- Plasma drug concentration–time curve should be available.

PHARMACOKINETIC EVALUATION OF THE DATA

- Area under the curve to the last quantifiable concentration (AUC0–t)
- Area under the curve to infinity (AUC0–∞)
- T max
- C max
- Elimination rate constant, k
- Elimination half-life, t 1/2

STATISTICAL EVALUATION OF THE DATA

(a) Analysis Of Variance (ANOVA) When $p \leq 0.05$, the difference b/w 2 drug products is not “statistically significant”.

(b) Two One-Sided Tests Procedure Demonstrate if bioavailability of the drug from Test formulation is too low or high in comparison to reference drug.

WAIVERS OF IN VIVO BIOEQUIVALENCE STUDIES

- Done when 2 drug products are:
- In same dosage form.
- Proportionally similar in active & inactive ingredients.
- Differ only in strengths of the medication.
- Bioequivalence study of lower strength(s) can be waived.
- Only in vitro dissolution test is required to establish bio-equivalency.

reference

1) Applied Biopharmaceutics and Pharmacokinetics, 7th Edition by Leon Shargel , Andrew B.C YU ; page no: 482 -488
2) Basic pharmacokinetics 2nd edition: by Sunil S Jambekar and Philip J Breen

   page no:- 141 - 155

Thank you