BIOEQUIVALENCE STUDY DESIGN

Seminar submitted to

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Introduction

- Bioequivalence (BE) is the absence of a significant difference in the rate and extent to which the active moiety in pharmaceutical equivalents or alternatives becomes available at the site of drug action when administered at the same molar dose under similar condition.

- It is determined by comparison of measured parameters like :
  1. Conc. of active drug ingredient in blood
  2. Urinary excretion rate
  3. Or pharmacodynamic effect

Objective

The drug bioavailability from test and reference product are not statistically different when administered to patients at same molar dose.

Study considerations

The basic design for bioequivalence study is determined by:

1. Scientific question and objectives to be answered
2. Nature of reference material and dosage form, to be tested
3. The availability of analytical methods
4. Pk and Pd of drug substance
5. Route of admn.
6. Benefit risk and ethical consideration(testing in humans)

Study designs

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 admn. of drug fasting continued up to 4 more hrs.
5. Blood sampling is performed before dose and at diff intervals after dose.
6. Plasma drug concentration-time profile is obtained.
7. No other medication given at least 1 week prior to study.

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 admn. 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.

Crossover study designs

1. Each subject receives the test and reference drug product.
2. Latin Square Crossover designs are used for BE study in human volunteers .
3. These Latin Square designs plans the clinical trials so that each subject receives each drug product only once.
4. Enough time between medications for elimination of drug is given.
5. Possible crossover effects are minimized by sequence or order in which drug products are given to subject.

Latin-Square Crossover Design for a Bioequivalence Study of Three Drug Products in Six Human Volunteers

	Drug Product		
Subject	Study Period 1	Study Period 2	Study Period 3
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	C	B	A
6	B	A	C

Latin-Square Crossover Design for a Bioequivalency Study of Four Drug Products in 16 Human Volunteers

	Drug Product			
Subject	Study Period 1	Study Period 2	Study Period 3	Study Period 4
1	A	B	C	D
2	B	C	D	A
3	C	D	A	B
4	D	A	B	C
5	A	B	D	C
6	B	D	C	A
7	D	C	A	B
8	C	A	B	D
9	A	C	B	D
10	C	B	D	A
11	B	D	A	C
12	D	A	C	B
13	A	C	D	B
14	C	D	B	A
15	D	B	A	C
16	B	A	C	D

	Period 1	Period 2
Sequence 1	T	R
Sequence 2	R	T

Period refers to the time period in which a study is performed
A two-period study is a study that is performed on two different days (time periods) separated by a *washout period* during which most of the drug is eliminated from the body—generally about 10 elimination half-lives.

A **sequence** refers to the number of different orders in the treatment groups in a study.
For example, a two-sequence, two-period study would be designed as above:
where R = reference and T = treatment.

The same reference and the same test are each given twice to the same subject. Other sequences are possible. In this design, Reference-to-Reference and Test-to-Test comparisons may also be made.

Replicated crossover study designs

1. When the no. of study subjects <80, it is difficult to achieve with highly variable drugs and drug product (%CV > 30).
2. These drugs have wide therapeutic window and despite high variability, have been demonstrated to be safe and effective.
3. Replicate designs for these drugs require smaller no. of subject and avoid exposure of large no. of healthy subjects.
4. Used for determining individual BE, to estimate within subject variance for both test and reference.
5. Provide an estimate of the subject- by- formulation interaction variance.

A four-period, two-sequence, two-formulation design is recommended by the FDA.

	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T

where R = reference and T = treatment.

The same reference and the same test are each given twice to the same subject. Other sequences are possible.

In this design, Reference-to-Reference and Test-to-Test comparisons may also be made.

Scaled average bioequivalence

1. 3 sequence, 3 period, 2 treatment partially replicated crossover design.
2. This design allows the estimation of within -subject variance and subject- by – formulation interaction for reference product.
3. Completion time of this study is shorter than fully replicated four way crossover.
4. If the test has lower variability than reference product, the study will need smaller no. of subjects.
5. This is evaluated for both AUC and C_{max}.

Scaled average bioequivalence

	period 1	period 2	period 3
Sequence 1	T	R	R
Sequence 2	R	T	R
Sequence 3	R	R	T

Non replicate parallel study design

1. For the drugs having long elimination half life or depot injection in which the drug is slowly released over weeks and month.
2. Two separate groups of volunteers are used.
3. One group will have the test product while the other will have the reference product.
4. Blood sample collection time should be adequate to ensure completion of GI transit(2-3days).
5. Cmax and AUC, 72 hrs after dose admn. can be used to characterize peak and total drug exposure.
6. This design is not for drugs that have high intrasubject variability in distribution and clearance.

Multiple dose (steady state) study design

1. Multiple doses of same drug are given consecutively to reach steady state plasma drug levels.
2. The multiple dose study is designed as steady state, randomized, 2 treatment, 2 way, crossover study comparing equal dose of test and reference.
3. To ascertain that the subjects are at steady state, three consecutive trough concentrations (C_{min}) are determined.

Pharmacokinetic analyses include calculation of following parameters for each subject:

AUC_{0-t} → Area under the curve during a dosing intervals

t_{max} → Time to C_{max} during a dosing interval

C_{max} → Maximum drug concentration during dosing interval

C_{min} → Drug concentration at end of a dosing interval

C_{avg} → The average drug concentration during a dosing interval

Degree of fluctuation = $(C_{max}-C_{min})/C_{max}$; Swing = $(C_{max}-C_{min})/C_{min}$

Clinical endpoint BE study

1. This consists of randomised double-blind, placebo-controlled, parallel-designed study comparing test product, reference product, and placebo product in patients.

2. The primary analysis for bioequivalence is determined by evaluating the difference between the proportion of patients in the test and reference treatment groups who are considered a “therapeutic cure” at the end of study.

3. The superiority of the test and reference products against the placebo is also tested during the same dichotomous end point of “therapeutic cure”.

Special Concerns in Bioavailability and Bioequivalence Studies

1. For certain drugs and dosage forms, systemic bioavailability and bioequivalence are difficult to ascertain for eg. cyclosporine, verapamil, are considered to be highly variable.
2. The number of subjects required to demonstrate bioequivalence for these drug products may be excessive, requiring more than 60 subjects.
3. The intrasubject variability may be due to the drug itself or to the drug formulation or to both.
4. The FDA has held public forums to determine whether the current bioequivalence guidelines need to be changed for these highly variable drugs.

Problems in Bioavailability and Bioequivalence

Drugs with high intrasubject variability	Inhalation
Drugs with long elimination half-life	Ophthalmic
Biotransformation of drugs	Intranasal
Stereo selective drug metabolism	Bioavailable drugs that should not produce peak drug levels
Drugs with active metabolites	Potassium supplements
Drugs with polymorphic metabolism	Endogeneous drug levels
Nonbioavailable drugs (drugs intended for local effect)	Hormone replacement therapy
Antacids	Biotechnology-derived drugs
Local anesthetics	Erythropoietin interferon
Anti-infectives	Protease inhibitors
Anti-inflammatory steroids	Complex drug substances
Dosage forms for nonoral administration	Conjugated estrogens
Transdermal	

Conclusion

Bioequivalence studies are performed to compare the bioavailability of the generic drug product to the brand-name product.

Bioequivalence can also be considered as performance measures of the drug product in-vivo. If the drug products are bioequivalent and therapeutically equivalent, then the clinical efficacy and the safety profile of these drug products are assumed to be similar and may be substituted for each other.

References

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Thank You