



**Centurion**  
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# **BIOEQUIVALENCE AND DRUG PRODUCT ASSESSMENT IN –VIVO**

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# INTRODUCTION

- Bioavailability and Bioequivalence studies provides important information in overall set of data that ensure availability of safe and effective medicines.
- The concept of bioavailability and bioequivalence have gained during last three decades.
- Now it has become very important for approval of brand name and generic drug worldwide.

## OBJECTIVES

- ❖ The most important objective is to measure and compare the formulation performance between two or more pharmaceutically equivalent drug product.
- ❖ To evaluate the absolute Bioavailability of dosage form compared with reference dosage form.
- ❖ Dose Proportionality Study to determine if Bioavailability parameters are linear over proposed dosage range.
- ❖ Intra/ Inter subject variability.
- ❖ Intervention study to examine effect of food and concomitant medications.

## Definition

➤ By United States Food and Drug Administration (USFDA) :

The absence of 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.

➤ By World Health Organization (WHO) :

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities in terms of rate ( $C_{max}$  and  $t_{max}$ ) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions are similar to such a degree that their effects can be expected to be essentially the same.

# Need of Bioequivalence

- The need of bioequivalence studies is increasing due to the large growth of the production and consumption of generic product
- Bioequivalence studies are conducted if there is :
  - A risk of bio inequivalence or
  - A risk of pharmacotherapeutic Failure
- No clinical studies have been performed in patient with generic product to support its efficacy and safety.
- In vivo Bioavailability / Bioequivalence studies are recommended to applicants intending to submit Investigational New Drug Application (INDA)/ New Drug Application (NDA)/ Abbreviated New Drug Application (ANDA) for conventional and extended release dosage forms administered orally.

# Types of Equivalence

## 1. Chemical Equivalence

Two or more drug Product contain same labelled chemical in a same amount.

## 2. Pharmaceutical Equivalence

Two or more drug are identical in strength, quality, purity, content uniformity, disintegration and dissolution.

## 3. Therapeutic Equivalence

Indicate that two or more drug product that contain the same therapeutically active ingredient elicit identical pharmacological effect and control the disease to the same extent

## 4. Bioequivalence

It is relative term which denotes that the drug substance in two or more identical dosage form reaches the systemic circulation at the same relative rate and relative extent.

## *Need of In vivo studies*

- Oral immediate release product with systemic action.
- Drug having Narrow Therapeutic margin
- Modified Release product with systemic action.
- Non oral immediate release product

## STATISTICAL EVALUATION OF Bioequivalence DATA

- Statistical evaluation studies is based on analysis of drug or plasma concentration.
- Area under the plasma concentration v/s time curve (AUC) is used as an index of extent of drug absorption.
- In the early 1970s, approval was based on mean data. Mean AUC and  $C_{max}$  values for the generic product had to be within 20% of those of the brand-name product.



# DESIGN AND EVALUATION OF BIOEQUIVALENCE STUDIES

## Study Designs

### Fasting Study

- Used for Immediate Release and modified release oral dosage form
- Overnight fast and 4 hour after dosing

### Food Intervention Study

- Co-administration of food with an oral drug product may affect the bioavailability of drug

### Multiple dose study

- Multiple dose, randomized, crossover study
- Three Consecutive trough concentration on three consecutive days.

# Types of Design

## 1. Complete Randomized Design

All treatment are randomly allocated among all experimental subject.

Example : If there is 20 subjects, number them from 1 to 20, Randomly select non repeating number.

- Advantages

1. Easy design
2. Can accommodate any number of treatment and subject.

- Disadvantages

All Subject must be homogenous.

## 2. Randomized Block Designs

- Subjects are sorted into homogenous groups called as blocks.
- Completely randomize block design mean that each block have all treatment and the treatments are randomize with all block.
- The treatments are assigning at random the experimental unit within each block.
- An extraneous source of validity (nuisance factor) is present.
- Nuisance factor is a design factor that probably has an effect on the response but we are not interested in that effect.

### Advantages

- i. Different treatment doesn't need equal sample size
- ii. Can accommodate any number of treatment.
- iii. Statistical analysis is relatively simple.

### Disadvantages

Degree of freedom is less

### 3. Repeated Measured, Cross over, carry over Designs

- Randomized Block Design
- Administration of two or more treatment one after the other is specified or random or random order to the same group of patient is called crossover design or change over design.

#### Advantages

1. Good precision for comparing treatments
2. Economic on subjects

#### Disadvantages

1. Order effect which is connected with the position in the treatment order
2. Carry over effect

## Crossover Parallel Design

A Parallel design is completely randomized design in which each subject receive one and only one formulation of the drug in a random fashion.

The simplest parallel design is two group Parallel design, which compares formulation of two drugs.

In this design each group contain equal number of subjects.

## Crossover Studies

Randomized complete block design of two subjects receiving four treatments.

Subjects	Period 1	Period 2
1	T	S
2	S	T

Randomized complete block design of six subjects receiving four treatments.

Subject 1	Period 1	Period 2	Period 3	Period 4
1	B	C	A	D
2	D	C	A	B
3	B	C	D	A
4	D	C	B	A
5	C	D	A	B
6	D	C	B	A

## Replicated cross over design

Used for determination of individual bioequivalence.

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

## Types of Evidence to Establish Bioequivalence

- Bioequivalence in descending order of accuracy, sensitivity and reproducibility.
- In vivo measurement of active moiety or moieties in biologic fluid
- In vivo pharmacodynamic comparison
- In vivo limited clinical comparison
- In vitro comparison
- Any other approach deemed appropriate by FDA.

# Evaluation of Data

- **Analytical Data**

Analytical method for measurement of drug must be validated for accuracy, precision, sensitivity and specificity.

More than one method during bioequivalence study may not be valid because different methods may yield different values



## Dosage Form Performance



Clinical Measurements

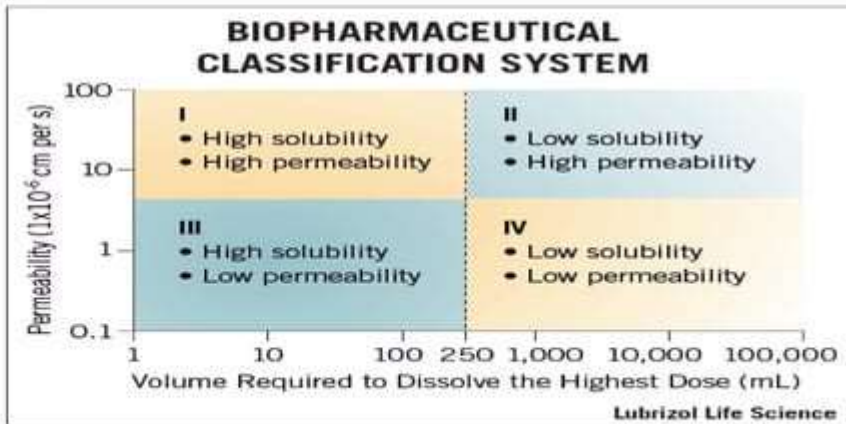
Pharmaceutical Measurements

## Biowaivers

- The term BIOWAIVER is applied to a drug regulatory approval process when a dossier (application) is approved based on the evidence of Bioequivalence
- The biowaiver means that the In vivo bioavailability and bioequivalence studies may be waived (i.e. not necessary for the product approval)
- In 1995, US Department of Health and Human Services and USFDA started the Biopharmaceutical Classification System with the aim of granting so called Biowaivers for SUPAC.
- Applicant can request biowaiver for immediate release product based on an approach termed as the Biopharmaceutics Classification System BCS.

- The BCS is a framework for classifying drug substances based on solubility and intestinal permeability.
- The BCS Classifies Drug Substance as:

Figure 1



A decorative graphic in the top-left corner consisting of two parallel lines forming an L-shape. The inner line is orange and the outer line is dark grey.

**Thank You !**