

Bioequivalence Studies

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Definition :-

- ❖ It refers to the drug substance in two or more identical dosage forms, reaches systemic circulation at the same rate and to the same relative extent.
- ❖ i.e. their plasma concentration-time profiles will be identical without significant statistical differences.

Advantages:-

- ❖ Minimizes the effect of inter subject variability.
- ❖ It minimizes the carry over effect.
- ❖ Requires less number of subjects to get meaningful results.

Disadvantages:-

- ❖ Requires longer time to complete the studies.
- ❖ Completion of studies depends on number of formulations evaluated in the studies.
- ❖ Increase in study period leads to high subject dropouts.
- ❖ Medical ethics does not allow too many trials on a subject continuously for a longer time.

Requirements/Objectives :-

- ❖ If a new product is intended to be a substitute for an approved medicinal product as a pharmaceutical equivalent or alternative, the equivalence with this product should be shown or justified.
- ❖ In order to ensure clinical performance of such drug products, bioequivalence studies should be performed.
- ❖ Bioequivalence studies are conducted if there is:
 - A risk of bio - inequivalence and/or
 - A risk of pharmacotherapeutic failure or diminished clinical safety.

❖ Some of the important terms relevant in this context will be defined.

❑ **Equivalence :-** It is a relative term that compares drug products with respect to a specific characteristic or function or to a defined set of standards.

➤ There are several types of equivalences.

A. Chemical Equivalence

B. Pharmaceutical Equivalence

C. Bioequivalence

D. Therapeutic Equivalence

A. Chemical Equivalence :- It indicates that two or more drug products contain the same labelled chemical substance as an active ingredient in the same amount.

B. Pharmaceutical Equivalence :- This term implies that two or more drug products are identical in strength, quality, purity, content uniformity and disintegration and dissolution characteristics. They may, however, differ in containing different excipients.

C. Bioequivalence :- It is a relative term which denotes that the drug substance in two or more identical dosage forms, reaches the systemic circulation at the same relative rate and to the same relative extent i.e. their plasma concentration-time profiles will be identical without significant statistical differences.

- When statistically significant differences are observed in the bioavailability of two or more drug products, **bioinequivalence** is indicated.

D. Therapeutic Equivalence :- This term indicates that two or more drug products that contain the same therapeutically active ingredient elicit identical pharmacological effects and can control the disease to the same extent.

Types Of Bioequivalence Studies:-

➤ Bioequivalence can be demonstrated either –

- *In vivo*, or
- *In vitro*.

In vivo Bioequivalence Studies :-

- The following sequence of criteria is useful in assessing the need for *in vivo* studies:
 1. Oral immediate-release products with systemic action-
 - Indicated for serious conditions requiring assured response.
 - Narrow therapeutic margin.

- Pharmacokinetics complicated by absorption < 70 % or absorption window, nonlinear kinetics, presystemic elimination > 70 %.
 - Unfavorable physiochemical properties, e.g. low solubility, metastable modification, instability, etc.
 - Documented evidence for bioavailability problems.
 - No relevant data available, unless justification by applicant that *in vivo* study is not necessary.
2. Non-oral immediate-release products.
 3. Modified-release products with systemic action.

➤ *In vivo* bioequivalence studies are conducted in the usual manner as discussed for bioavailability studies, i.e. the pharmacokinetic and the pharmacodynamic methods.

1. Pharmacokinetic Methods

- a) Plasma level-time studies
- b) Urinary Excretion studies

2. Pharmacodynamic Methods

- a) Acute pharmacological response
- b) Therapeutic response

In vitro Bioequivalence Studies :-

- If none of the above criteria is applicable, comparative *in vitro* dissolution studies will suffice.
- *In vitro* studies, i.e. dissolution studies can be used in lieu of *in vivo* bioequivalence under certain circumstances, called as *biowaivers(exemptions)*-
 1. The drug product differs only in strength of the active substance It contains, provided all the following conditions hold –
 - Pharmacokinetics are linear.

- The qualitative composition is the same.
- The ratio between active substance and the excipients is the same, or (in the case of small strengths) the ratio between the excipients is the same.
- Both products are produced by the same manufacturer at the same production site.
- A bioavailability or bioequivalence study has been performed with a original product.
- Under the same test conditions, the *in vitro* dissolution rate is the same.

2. The drug product has been slightly reformulated or the manufacturing method has been slightly modified by the original manufacturer in ways that can convincingly be argued to be irrelevant for the bioavailability.

3. The drug product meets all of the following requirements –
 - The product is in the form of solution or solubilised form (elixir, syrup, tincture, etc).

 - The product contains active ingredient in the same concentration as the approved drug product.

- The product contains no excipients known to significantly affect absorption of the active ingredient.
4. An acceptable IVIVC and the *in vitro* dissolution rate of the new product is equivalent with that of the already approved medicinal product.

Moreover,

- The product is intended for topical administration (cream, ointment, gel, etc.) for local effect.
- The product is for oral administration but not intended to be absorbed (antacid or radio-opaque medium).

- The product is administered by inhalation as a gas or vapour.
- The criteria for drug products listed above indicate that bioavailability and bioequivalence are self-evident.

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Thank You