UNIT

XII

BIOEQUIVALENCE STUDIES

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INTRODUCTION

Generic formulation must fulfil the same quality standards as brand-name formulation or originators formulation. A generic product's manufacturer must show that it meets the following criteria:

- Same quality requirements as the innovator product.
- Ensure that it is clinically interchangeable with the originator product, i.e. therapeutically identical or bioequivalent.

Therefore, the manufacturer may have to conduct a bioequivalence study: the results should be able to fill the gap between the innovator product, which has safety and efficacy data, and the generic product, which do not.

BIOEQUIVALENCE STUDIES: NEED AND GOALS

Equivalence studies of pharmaceutical product should be done if a new product is intended to be a pharmacological equivalent or alternative to an approved originators product. If there is a risk of bio-inequivalence, pharmacotherapeutic failure, or decreased clinical safety, bioequivalence studies are done.

SOME KEY TERMS CRUCIAL TO THIS TOPIC WILL BE DEFINED.

Equivalence is a relative phrase that evaluates drug formulation against a predetermined set of standards or a specific property or function. Equivalences come in a variety of forms:

Chemical Equivalence refers to the presence of the same labelled chemical substance as an active component in the same amount in two or more drug formulations.

Pharmaceutical Equivalence: This phrase refers to the strength, quality, purity, content uniformity, and disintegration and dissolving properties of two or more pharmaceutical formulations; nevertheless, they may differ in excipient content.

Therapeutic Equivalence means that two or more drug products formulation with the same therapeutically active ingredient have the same pharmacological effects and may control the disease to the same degree.

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Bioequivalence: Two formulation are said to be bioequivalence when the active pharmaceutical ingredient in two or more identical dosage forms, reaches the systemic circulation at the same relative pace and to the same relative extent meaning their plasma concentration-time profiles will be identical without significant statistical deviations.

Bio-inequivalence is defined as statistically significant differences in the bioavailability of two or more drug formulation.

TYPES OF STUDIES REQUIRED IN BIOEQUIVALENCE STUDIES

In-vivo Bioequivalence Studies

A bioequivalence study or a comparative clinical pharmacodynamic study were used to determine in-vivo equivalence for some drugs. For an "oral immediate release formulation with systemic action" having narrow therapeutic window, nonlinear pharmacokinetics, > 70% presystemic elimination, steep dose-response curve, poor physicochemical properties of drug like, low solubility, instability etc.. In-vivo testing is also used to evaluate "non-oral instant release products" like vaginal tablets and "modified release products with systemic action" like enteric coated tablets.

In-vitro Bioequivalence Studies

Only in-vitro dissolution study data can be utilised instead of in-vivo bioequivalence under the following criteria,

1. Only the potency of two or more drug formulation differs,
2. Manufacturing methods differ substantially
3. The drug formulation is in solution form (elixir, syrup, tincture, etc.)
4. The new product has a satisfactory IV-IVC and in-vitro dissolution rate

PHARMACOKINETIC STUDIES: DESIGN AND EXECUTION

a) Study object

The study protocol is determined by the bioavailability study's goal. A bioequivalence study comparing the test formulation to the

standard formulation differs from a study methodology used to estimate pharmacokinetic parameters.

b) Research design

The primary goal of the experimental design is to reduce the number of experimental variables while avoiding bias. The following factors are considered when conducting an in vivo bioavailability study:

1. Completely randomized designs

In a completely randomised design, all treatments (factor levels) are randomly allocated among all experimental subjects.

Method of randomisation: Label all subjects with the same number of digits, for e.g., if there are 20 subjects, number them from 1 to 20. Randomly select non-repeating random numbers (like simple randomisation) with among these labels for the first treatment, and then repeat for all other treatments.

Advantages: easy to construct design, accommodate any number of treatments and subjects, easy and simple to analyze.

Disadvantages:

- Although the approach can be utilised for any number of treatments, it works best in scenarios with a limited number of groups.
- All subjects should be as similar as feasible. Any additional sources of variability will tend to increase the random error term, making it difficult to identify differences in mean responses between treatments (or factors).

2. Randomized block designs

Initially, the participants are divided into homogeneous groups called blocks. Then, the groups are treated randomly within the block.

Randomization method: Blocks are established by subjects with comparable background features. Then, exactly like with simple randomization, treatments are assigned to each block at random. Different blocks are randomly generated independently of one another.

Advantages: Easy to design scheme with comparatively simple data analysis, produce far more exact results, can accommodate any number of treatments, and removal of a block for any reason has no effect on analysis.

Disadvantages:

- Missing data within a block necessitate a more extensive analysis.
- The degrees of freedom of experimental error are not as great as they are in a completely randomized design.

3. Repeated measures, cross-over and carry-over designs

The same subject acts as a block in this randomised block pattern. Each of the treatments under investigation uses the same subject. The repeated measures design gets its name from the fact that we conduct repeated measurements on each subject. The study could include many treatments or a single treatment that is examined at different times. A crossover design or change-over design is when two or more treatments are given to the same group of patients one after the other in a predetermined or random order.

Randomization method: The order of treatments for each patient is randomised using complete randomization. Different subjects' randomizations are independent of one another.

Advantages:

- Because all causes of variability between patients are removed from the experimental error, they give good accuracy for assessing treatments.
- It is cost-effective in terms of subjects. This is especially crucial when there are only a few volunteers available for the experiments.
- When studying the effects of a treatment over time, it is usually preferable to watch the same subject at different times rather than multiple subjects at the specified times.

Disadvantages:

- There could be an order impact, which is linked to the treatment order position.

- There could be a carry-over impact that is linked to the previous treatment or therapies.

4. Latin square designs

Completely randomised design, randomised block design and repeated measures design are experiments in which the person/subject/volunteer is treated from the beginning to the completion of the experiment. Hence, this design is also known as "continuous trial". However, in a Latin square, each group receives each treatment throughout the experiment. A Latin square design is a two-factor design with one observation in each cell (subjects and treatments are the two factors). When three or more treatments are to be compared and carry-over effects need to be balanced, this design is preferable to the previous ones. Rows indicate subjects, while columns represent treatments in a Latin square pattern. Each of the r2 cells in a r x r Latin square design contains one and only one of the r letters indicating the therapies, and each letter appears once and only once in every row and column. If the first row and column of a Latin square contain the letters r in alphabetical order, it is considered standard.

Advantages:

- It reduces the variability in plasma drug levels between subjects.
- Reduces the possibility of carry-over effects when a given dose form alters the bioavailability of a later administered substance (intra-subject variability).
- Reduces fluctuations caused by the passage of time.
- A small-scale experiment can be used to investigate treatment effects. This is especially useful in exploratory or pilot research.
- Allows for a greater focus on formulation variables, which is critical to the outcome of any bioequivalence investigation.

Disadvantages-

- When only a few treatments are tested, the adoption of Latin square design will result in a very small number of degrees of freedom for experimental error. When multiple treatments are investigated,

however, the degrees of freedom for experimental error may be greater than necessary.

- The randomization required is a little more complicated than in previous designs.
- The study takes a long time since an adequate washout interval between two administrations is required, which might be rather long if the drug has a long half-life.

WAIVERS OF IN VIVO BIOEQUIVALENCE STUDIES

The phrase "biowaiver" refers to a regulatory drug approval process in which the safety and effectiveness portions of a dossier (application) are accepted based on proof of equivalent other than in vivo equivalency testing.

If a drug product fits one of the following requirements, a drug manufacturer may request that the US-FDA waive the requirement for *in vivo* bioequivalence testing.

- If a drug formulation is intended for parenteral administration by injection, and includes the active pharmaceutical ingredient in the same concentration and in same solvent as that of originators formulation.
- The generic product is intended for topical application (e.g. otic or ophthalmic solution), or it is inhaled and contains the active pharmaceutical component in the same dosage form as the original formulation.
- The drug product is a topical solution, an oral solution, a syrup, elixir, tincture, a solution for nebulization, a nasal solution, or a similar other solubilized form that incorporates an active drug ingredient in the same concentration and dosage form as the drug product that is the subject of an approved full NDA and ANDA and contains no inactive ingredient or other formulation change that may significantly affect absorption of the active drug ingredient.
- Biowaivers may be feasible for solid oral dosage forms (other than controlled release or enteric-coated) based on the Biopharmaceutics Classification System (BCS) or the proportionality of a product's

formulation to the formulation of another strength of that product (an additional strengths biowaiver).

- In the case of some therapeutic items, information collected in vitro can be used to demonstrate bioavailability or bioequivalence instead of in vivo data. If a drug product fits the following requirements, the FDA may waive the requirement for in vivo data submission:

    1. The drug formulation is in the same dosage form as another drug product from the same manufacturer, but in a different strength, and has active and inactive substances that are proportionally equal.
    2. The drug product has been proved to pass an in vitro test that ensures bioavailability,
    3. The drug product for which FDA has merely required in vitro bioequivalence data for approval.

CONCLUSION

Over the last two decades, the pharmaceutical industry and national regulatory bodies around the world have embraced the concept of bioavailability and bioequivalence research. It is mostly due to the rise in the number of generic medications and their formulations that are commercialised following regulatory approval. As a result, bioavailability and bioequivalence studies followed strict protocols and were changed as needed. Statistical approaches are used to analyse pharmacokinetic parameters in order to obtain reliable results and provide high-quality interchangeable and inexpensive medications. Different businesses, authorities, and fundamental scientists are continually attempting to comprehend and build more efficient and scientifically valid approaches to evaluating bioavailability and bioequivalence studies of various formulations.

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