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Original Article

A REVIEW ON DESIGN, EVALUATION AND NEED OF BIOEQUIVALENCE STUDY

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ABSTRACT

Generics are of high significance in the countries where intellectual property laws are stringent. Once drug patent expire, monopoly of the innovator comes to end and generic drugs having the same formula as the brand-name drug are marketed at a much lower price. These drugs offer great advantage of being economical, as there is no significant change in the quality of the patient care and huge cost saving. Regulatory authorities Food and Drugs Administration (FDA) and European Medicines Agency (EMEA) insist that generic products should compulsorily be "essential similar" with that of reference product in order to exclude any clinically significant difference. Comparing brand-name drug, the generic drug must have similar composition (same quality and type of active principle), route of administration and therapeutic equivalence (bioequivalence). The design and evaluation of bioequivalence study require the preferred approach is an in-vivo study carried out in healthy volunteers to whom the 2 preparations (generic and innovator) are alternatively administered and also require the cooperative input from pharmacokinetic scientist, statistician, bio-analytical chemists and others.

Keywords: Innovator Drugs, Generic Drugs, Bioequivalence

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1.0 INTRODUCTION

Introduction of generic drugs into the market as these produce immense saving to nation economy[1]. Thus, they have to play an important role in holding down national spending on prescription drugs. Generics are of high significance in the countries where intellectual property laws are stringent[2,3].

Once drug patent expire, monopoly of the innovator comes to end and generic drugs having the same formula as the brand-name drug are marketed at a much lower price. These drugs offer great advantage of being economical, as there is no significant change in the quality of the patient care and huge cost saving[4].

Regulatory authorities Food and Drugs Administration (FDA) and European Medicines Agency (EMEA) insist that generic products should compulsorily be "essential similar" with that of reference product in order to exclude any clinically significant difference. Comparing brand-name drug, the generic drug must have similar composition (same quality and type of active principle), route of administration and therapeutic equivalence (bioequivalence).

Many important drugs like diclofenac sodium[5], theophylline[6], phenytoin[7], warfarin tablet[8], digoxin tablets[9] and levothyroxine tablets[10] have failed bioequivalence studies.

This danger is of much concern in the developing countries like India where quality of the drugs is always questionable and also there is not much data available on the bioequivalence studies of marketed drugs[11]. In India, large number of small scale pharmaceutical industries (>20,000) are engaged in drugs manufacturing which have inadequate facility and little concern to follow Good Manufacturing Practice (GMP) guidelines.

1.1 Bioequivalence study: Design and Evaluation

The preferred approach is an in-vivo study carried out in healthy volunteers to whom the 2 preparations (generic and innovator) are alternatively administered. The design and evaluation of well controlled bioequivalence studies require the cooperative input from pharmacokinetic scientist, statistician, bio-analytical chemists and others.

1.2 Design

The design of a bioavailability and/or bioequivalence study is dependent upon the drug, dosage form and study objectives. For BE trial, both the test and reference drug formulations contain the pharmaceutical equivalent drug in the same dose and are given by the same route of administration. A pilot study in small number of subjects can be carried out before proceeding with

a full BE study. This study can be used to validate analytical methodology assess variability, optimize sample collection time intervals, and provide other information. Non-replicate crossover study designs are recommended by FDA (CDER, 2003) for immediate release and modified-release dosage forms. However, replicate designs can also be used. The recommended method for analysis to establish BE is average bioequivalence. The study should be crossover design and suitably randomized, as far as possible. Some of designs are being discussed below[12].

1.3 Two-Period Crossover Design

In case of two formulations, an even number of subjects should randomly divide into two equal groups. In the first period, each member of one group will receive a single dose of the test formulation and each member of the other group will receive a standard formulation. After a suitable washout period (not less than 5 half lives), each member of the respective groups will receive a single dose of an alternative formulation and experiment will be repeated in the second period.

Table: Two-Period cross over design

Group No.	Subjects in Group	Treatment for period No.	
		I	II
1.	1,2,3,4,5,6	A	B
2.	7,8,9,10,11,12	B	A

1.4 Latin Square Design

In case of more than two formulations, a Latin square design should be used. In this design each subject receives each formulation in cross over design and therefore mostly number of periods are equal to number treatments.

Table: Latin square design

Group No.	Subjects in Group	Treatment for period No.		
		I	II	III
1.	1,2,3,4,5,6	A	C	B
2.	7,8,9,10,11,12	B	A	C
3.	13,14,15,16,17,18	C	B	A

1.5 Balance Incomplete Block Design

In case there are more than three formulations, the Latin square design will not be ethically advisable, mainly because each volunteer may require the drawing of too many blood samples. However, if each volunteer is expected to receive at least two formulations, then such a study can be carried out using Balance Incomplete Block Design as represented in table 3. As per this design, if there are four formulations, six possible pairs of formulations can be chosen from four formulations. Then, the first six volunteers will receive these six pairs of formulations and the next six volunteers will receive the six pairs in reverse order.

Table 3: Balance Incomplete Block Design

Subject No.	Treatment For period number	
	I	II
1.	A	B
2	A	C
3.	A	D
4.	B	C
5.	B	D
6.	C	D
7.	B	A
8.	C	A
9.	D	A
10.	C	B
11.	D	B
12.	D	C

1.6 Statistical issue in BE studies

The pharmacokinetic parameters, C_{max}, T_{max} and AUC should be subjected to three-way analysis of variance (Three-way ANOVA) in order to test differences due to formulations, period and subjects. A more complex ANOVA may be appropriate in some circumstances, e.g. if treatments are replicated. The standard parametric ANOVA assumes homogeneity of variance, normality and additivity of independent variables.

In order to ensure homogeneity of variances between treatments, Barttlet's test or a similar test should be carried out prior to performing the ANOVA. The primary comparison of interest in bioequivalence study is the ratio of average parameter data (AUC or C_{max}) from the test and reference formulation rather than the difference between them. Log transformation of the data allows the general linear statistical model to draw interferences about the ratio of the two averages on the original scale. Log transformation thus achieves the general comparison based on the ratio rather than on the difference.

Moreover, plasma concentration data, including AUC and C_{max}, tend to be skewed and their variances tend to increase with the means. Log transformation corrects this situation and makes the variances independent of the mean. Further, the frequency distribution skewed to the left, i.e., those with a log tail to the right is made symmetrical by log transformation. In case suitable transformation is available, the non-parametric method should be used. T_{max} values being discrete should be analyzed using non-parametric methods.

1.7 Two one sided test procedures

This procedure is also referred to as confidence interval approach. This method is used to demonstrate if the bioavailability of the drug from the test formulation is too high or low in comparison to the reference drug product. The 90% confidence limits are estimated for the sample means. In this test, presently required by the FDA, a 90% confidence interval about the ratio of means of the two products must be within $\pm$ 20% for the measurement of the rate and extent of drug bioavailability. The lower 90% CI for the

ratio of means cannot be less than 0.8, and the upper 90% CI for the ratio of the means cannot be grater than 1.20. The 90% CI is a function of sample size and study variability, including inter and intra subject variability. Table 4 mentions the bioequivalence criteria followed by various regulatory agencies in the world.

Table 4: Bioequivalence criteria of various regulatory agencies

Bioequivalence requirements of regulatory agencies				
Parameter	**EMEA**	**USFDA**	**CANADIAN TPD**	**CDSCO**
Log transformed C_{max} using 90% CI	80-125% of reference.	80-125% of reference.	The relative mean measured C_{max} should be between 80-120% of reference.	80-125% of reference.
Log transformed AUC_{0-t} using 90% CI	80-125% of reference	80-125% of reference	The relative mean measured AUC_{0-t} should be between 80-125% of reference	80-125% of reference

1.8 Need for bioequivalence

1.8.1 Generics

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength and route of administration, quality, performance characteristics and intended use[13]. A generic drug is produced and distributed without patent protection. The generic drug may still have a patent on the formulation but not on the active ingredient[14]. A generic must contain the same active ingredients as the original formulation.

1.8.2 Regulatory guidelines

Regulatory authorities (FDA, EMEA) insists that generic products should compulsorily be "essential similar" (composition, formulation and bioequivalence) with that of reference product in order to exclude any clinically significant difference. When two formulations of the same drug present similar bioavailability to the extent that they are considered bioequivalent by prescribed criteria, it is assumed that when administered in the same molar dose, they will provide the same therapeutic effect (therapeutically equivalent). Therapeutic equivalence could require extensive efficacy and safety studies but an equivalence study with enough power is considered sufficient. Regulatory bodies suggest that a new product can be substituted for an approved medicinal product (pharmaceutical equivalent or alternative) only if the equivalence with this product has been demonstrated or justifies. The use of generic drugs is of increasing importance in terms of

efficiency and in the selection of therapeutic alternatives.

1.8.3 Abbreviated New drug Application[15]

An Abbreviated New drug Application (ANDA) is an application for a U.S. generic drug approval for an existing licensed medication or approved drugs. ANDA contains data which when submitted to FDA's centre for Drug Evaluation and Research, Office of Generic drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

Generic drug applications are termed as "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e. performs in the same manner as the innovator drug).

Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug Price Competition and Patent Term Restoration Act of 1984," also know as the Waxman-Hatch Act.

1.8.4 Need of generic products

Generic manufacturers are able to offer products at lower prices than brand name products because they do not have to duplicate the cost of research and marketing conducted by the original manufacturer. Sales of generics in Canada were $1.44 billion in 2001 with provincial drug plans being major buyers. Generics represent approximately 40% of all prescriptions and 15% of drug costs. New generic drugs are typically introduced at prices that are 70% of comparable branded drugs[16].

Generic drugs can save patients and insurance companies substantial costs. The principal reason for the relatively low price of generic medicines is that competition increases among producers when drugs no longer are protected by patents[14].

Generic drugs can be produced when[14]

- The patent has expired of the innovator's product.
- The generic company certifies the brand company's patents are either invalid, unenforceable or will not be infringed.
- For drugs which have never held patents.
- In countries where a patent(s) is/are not in force.

Most nations require generic drug manufacturers to prove that their formulation exhibits bioequivalence to the innovator product.

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