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REVIEW ARTICLE **OPEN ACCESS**

A Review on Comprehensive Bioequivalence and Bioavailability Studies of Diabetic Drugs

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ABSTRACT

Bioequivalence have caught attention for the last three decades making its point that drug products which are in market with same quantities of the drug may show marked variances in in terms of therapeutic effects, making it difficult for Health care providers in selecting therapeutically equivalent drug products for the patients. In India, large number of patient's population falls under the category of economical and socially poor groups who hardly can afford the brand drugs and as a result, low compliance is noted. Government hospitals have generic drugs supplies but the authenticity in terms of pharmacokinetics and dynamics is of a concern. In India, very few studies have been focused on diabetes care and provide an insight into the current profile of patients and their management specially when it comes to clinical study (BA/BE studies). More than 50% of people with diabetes have poor glycaemic control, uncontrolled hypertension and dyslipidaemia, and a huge percentage have diabetic vascular complications. Considering the meagre availability and ability of the people to afford, it is unquestionably important that the generic drugs should be made obtainable so as to minimized the treatment. The present paper summarizes the requirements and guidelines to perform bioequivalence and bioavailability study of certain Diabetic drugs and to discuss the prescribing pattern of diabetic drugs.

Keywords: *Branded, Generic, Bioavailability, Bioequivalence, Study Designs, Diabetic drugs*

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INTRODUCTION

The term bioequivalence is used in pharmacokinetics to measure (expected) in vivo biological equivalence of two registered drug preparations. If two drugs are called bioequivalent than it means that they would be anticipated to be the same for all its objectives and purposes. In determining bioequivalence between two drugs such as a Brand drug (reference drug) and marketed generic drug (test drug), pharmacokinetic studies are carried out where brand as well as generic drugs are administered in a cross over study to healthy volunteers [1]. Blood (Serum/plasma) are collected at regular intervals and assayed for parent drug (constituents) concentration. The data of the plasma concentration are used to evaluate key pharmacokinetic parameters such as peak concentration (Cmax), time to peak concentration (Tmax), area under the curve (AUC) and absorption lag time (tlag). Bioequivalence will be recognized, if 90% confidence interval are within 80.00% to 125.00% for the ratio of the geometric least square means of natural log transformed Cmax, AUC0-t and AUC0-inf of Test and Reference drugs [2].

In India, the fundamental responsibility of CDSCO is to ensured efficacy and safety, uniformity in standards of quality of pharmaceutical products. Realistic assurance providing that the various products which contains equal active ingredients, marketed by certain licensees, are clinically equal and substitutable, therefore bioavailability and bioequivalence data is essential to be furnished liable on the type of request being submitted with applications for new drugs, under Schedule Y [3]. "Bioavailability as well as bioequivalent emphasis on the drug release from its dosage form and ensuing the drug absorption into the systemic circulation.'' Generally, it is documented be using the systematic exposure profile which is obtained by measuring the metabolite concentration in the systemic circulation over time and the profile which was obtained determined in early drug development phase (clinical trial) may be serve as a standard for successive bioequivalent studies (Committee for Medicinal Products for Human Use,2010) [4].

BIOAVAILABILITY EVALUATION

Usually, bioavailability is assessed by defining the area under the plasma concentration–time curve. The most dependable measure of a drug's bioavailability is Area Under Curve (AUC), which is directly proportional to the total amount of unchanged drug that reaches systemic circulation [5].

If the drug plasma concentration curves are fundamentally superimposable than drug products may be regard as bioequivalent in terms of extent and rate of absorption and is illustrated below in the diagram.

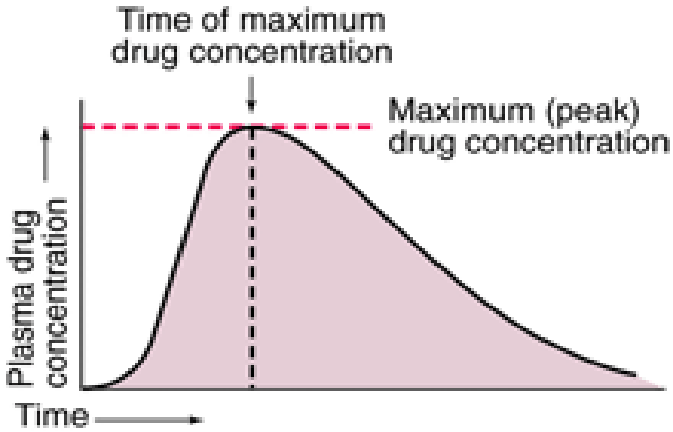

Figure 1: Plasma concentration–time relationship after a single oral dose of a hypothetical drug

Concentration of drug plasma rises with extent of absorption; the maximum concentration of plasma is reached when drug absorption rate equals drug elimination rate. Determinations of bioavailability which is based on the peak plasma concentration may be ambiguous because as soon as drug enters the bloodstream it starts elimination as well. Peak time is the most commonly used general index of absorption rate which shows the slower the absorption, the slower the peak time.

Excretion of drug primarily unaffected in urine, bioavailability can be assessed by measuring the total amount of drug excreted after a single dose. Preferably, urine is collected over a period of 7 to 10 elimination half-lives of drug for complete urinary recovery of the absorbed drug.

In recent decades, India has seen a steadily escalating diabetes epidemic. In reality, India now has the world's second-largest population of diabetics. According to the International Diabetes Federation (IDF), India has 72.9 million diabetics in 2017, with that number expected to grow to 134.3 million by 2045. (ICMR). Diabetes prevalence in urban India, especially in major metropolitan cities, has risen from 2% in the 1970s to over 20% today, with rural areas catching up quickly. (International Council on Medical Research)

PHARMACOLOGICAL MANAGEMENT OF DIABETES

Diabetes mellitus is a condition where there is disorder in the metabolism of carbohydrates, lipids and proteins [6] after a period of time, it is usually accompanied by complications like neuropathic, micro and macro vascular [7]. It is all due to inappropriate usage of insulin by the specific target cells or inadequate secretion of insulin by the pancreas [6].

Minimizing or avoiding complications arising from diabetics is the main thing in the management of diabetes and to avoid severe hypoglycemia / hyperglycemia including limb amputation, heart burn and blindness. It can all be prevented in those patients with only insignificantly reduced tolerance of blood glucose [8].

Glucose-Lowering Agents

Oral Hypoglycaemic Drugs: When a person's fasting glucose level surpasses 1600mg/L than is indicated for treatment of diabetes. For management of type II diabetes mellitus, the oral glucose-lowering drugs are used [6]. Presently, six classes of oral antidiabetic drugs (OADs) are available: sulfonylureas (e.g., glimepiride), biguanides (e.g., metformin), α-glucosidase inhibitors (e.g., acarbose), thiazolidinediones (e.g., pioglitazone), meglitinides (e.g., repaglinide), and dipeptidyl peptidase IV inhibitors (e.g., sitagliptin)

Insulin therapy: When a patient's glycaemic control is obtained at highest doses of oral therapy than insulin in being included for the treatment. Number of diabetologists choose insulin therapy to inductee when the patient is diagnosed with type II diabetes [9].

Guidelines

It is essential to regulated bioavailability and bioequivalence studies to ensure equivalence therapeutically between reference and test drug. Quite a few in vivo and in vitro methods are used to measure product quality.

Types of studies required when Bioequivalence studies is required:

In Vivo Studies

For certain drugs and dosage forms, *in vivo* documentation of equivalence, through either a bioequivalence study, a comparative clinical pharmacodynamic study, or a comparative clinical trial, is regarded as especially important. These include:

1. Oral immediate release drug formulations with systemic action
2. Non-oral and non-parenteral drug formulations design to be systematic absorption such as transdermal patches, suppositories,etc.
3. Sustained or otherwise modified release drug formulations designed to act by systemic absorption.
4. Non-solution pharmaceutical products which are for non-systemic use like oral, dermal, nasal, rectal, vaginal, etc. application and are envisioned to act without systemic absorption.
5. Fixed-dose combination drug with systemic action.

In vitro studies

By the use of in-vitro dissolution testing in following circumstances equivalence may be assessed.

a. Drugs for which the applicant provides data to verify all of the following:

i. highest dose strength is soluble in 250 ml of an aqueous media over the pH range of 1-7.5 at37°C

ii. at least 90% of the administered oral dose is absorbed on mass balance determination or in comparison to an intravenous reference dose

iii. speed of dissolution as demonstrated by more than 80% dissolution within 15 minutes at 37°C using IP apparatus 1, at 50 rpm or IP apparatus 2, at 100 rpm in a volume of 900 ml or less in each of the following media:

1. 0.1 N hydrochloric acid or artificial gastric juice (without enzymes)
2. a pH 4.5buffer
3. a pH 6.8 buffer or artificial intestinal juice (without enzymes)

b. Different strengths of the drug manufactured by the same manufacturer, where all of the following criteria are fulfilled:

i. the qualitative composition between the strengths is essentially the same;

ii. the ratio of active ingredients and excipients between the strengths is essentially the same, or, in the case of small strengths, the ratio between the excipients is the same;

iii. The method of manufacture is essentially the same;

iv. An appropriate equivalence study has been performed on at least one of the strengths of the formulation and

v. In case of systemic availability - pharmacokinetics have been shown to be linear over the therapeutic dose range.

In vitro dissolution testing may also be suitable to confirm unchanged product quality and performance characteristics with minor formulation or manufacturing changes after approval.

STIPULATION FOR BIOAVAILABILITY AND BIOEQUIVALENT STUDIES

Bioavailability studies delivers information regarding the science of kinetics (Absorption, Distribution, Metabolism and Elimination) of the new drug formulation, new dosage form such as fraction of drug absorbed, linearity, and non-linearity in the pharmacokinetics of the drug and proportionality of the dose, execution of the formulation [10]. It helps to establish dosage regimen. Bioequivalence studies are achieved for the comparison of two curative products comprising of the same active ingredient, two marketed products by different licenses consisting of the same active constituents or may be for another therapy [11]. The manufacturer must make sure that the post approval changes which are change in the supplier of the active ingredient, change in the manufacturing location or a change in the formulation does not change the drug product performance and is same for the change by conducting a bioequivalence study [12]. The performance of drug product may be resolute *in vivo* by BE studies or *in vitro* by comparative drug release or dissolution profiles, the schematic flow is shown in Fig. 2.

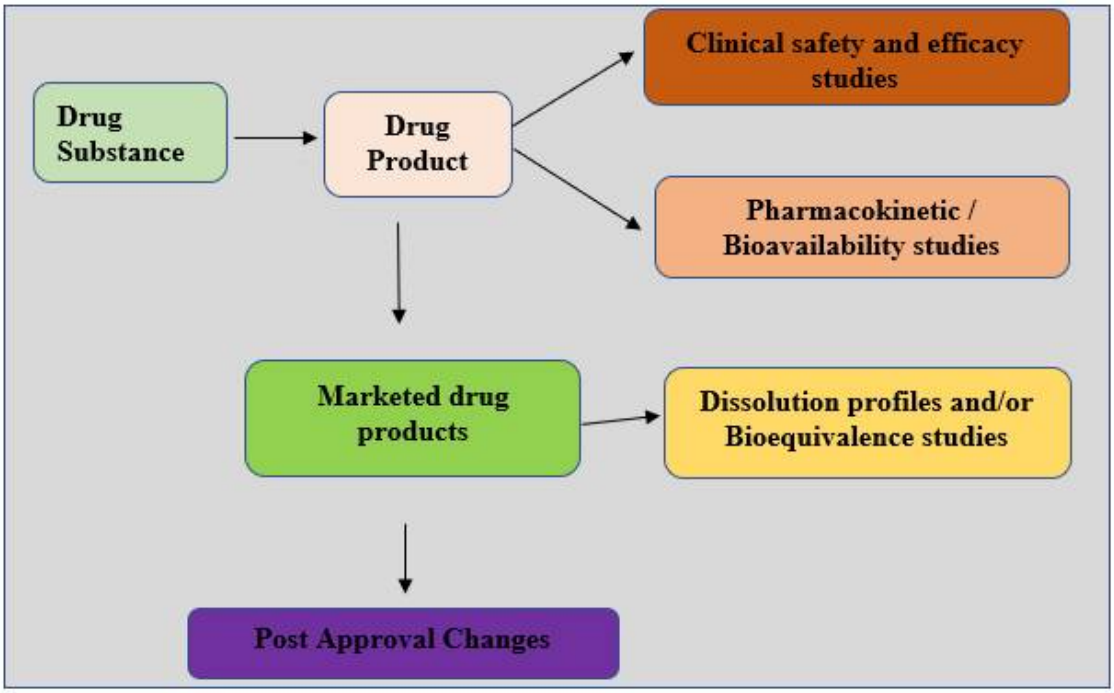

Figure 2: New drug product development and Drug product performance (Swain et al,2015)

Comparative drug product performance is important in development of generic products is presented in fig 3.

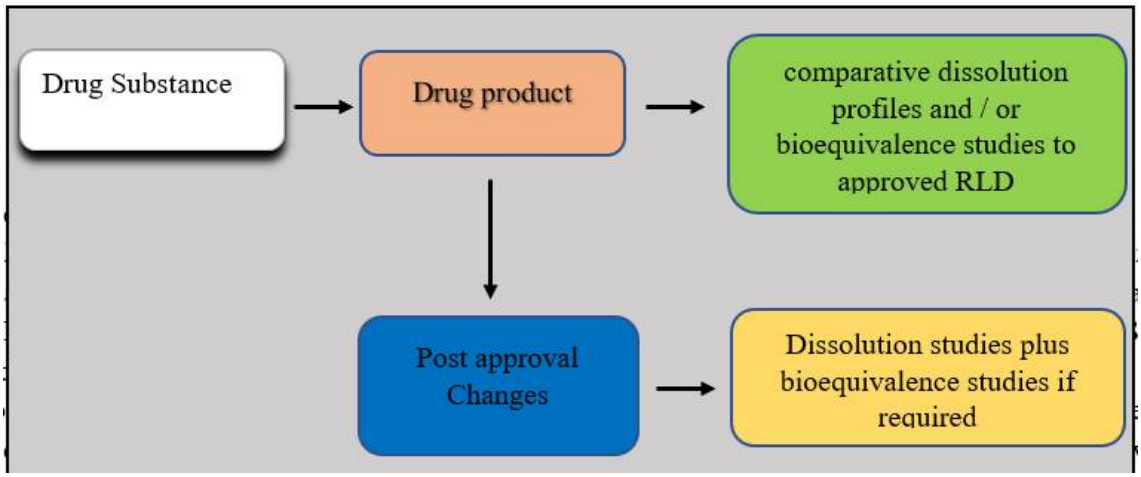

Figure 3: Drug product performance and generic drug product development (Swain et al,2015)

ETHICAL GUIDING PRINCIPLE IN CLINICAL STUDY

In clinical research, ethics emphases chiefly on identifying and applying the acceptable conditions for acquaintance of some persons to risks and burdens for the benefit of the society at huge [13]. In February 1980, Indian Council Medical Research (ICMR) released a 'Policy Statement on Ethical Considerations involved in Research on Human Subjects.' Early 1980's, scientists at the Institute for Cytology and Preventive Oncology in New Delhi conducted a study on cervical dysplasia or precancerous lesions of the cervix (Infochange india) and after the study, the patients were untreated and resulted in invasive cancer. In 1997, the study became a controversial topic thereafter ICMR initiated on developing 'Ethical Guidelines for Biomedical Research on Human Subjects' and got finalised in the year 2000. In one of the technical meeting of Central Drugs Standard Control Organization (CDSCO) led by Drug controller general came to a decision that Institutional Ethics Committee (IEC) would be reviewing and approving a protocol of any clinical trial. Additional, apex committee recommends that the practice of reviewing and approving protocols of BA/BE study by Independent Ethics Committees should be withdrawn. Well along the committee then decided that Independent Ethics Committee would be allowed for reviewing and approving only protocols for BA/BE studies of approved drug molecules [14]. CDSCO has approve

Institutional Ethics Committee Registration as per its anew introduced rule 122D.In 1964, the World Medical Association Declaration of Helsinki accentuated 12 basic principles for the conduct of human biomedical research shown in Fig. 4 (WMA).

Figure 4: Ethical guidelines for using humans in clinical trials

LITERATURE REVIEW

In one of the studies in Nigeria, the marketed generic metformin tablets were assessed for its bioequivalence using guidelines of British and United States Pharmacopoeia in healthy volunteers against the innovator drug in an open-label, two treatment and two arm crossover manner with a 7days washout time. At time interval of 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 h post-dose blood samples were collected and analysed by high-performance liquid chromatography method, and using the non-compartmental approach the pharmacokinetic parameters were attained. As a result, 9 metformin generics happened to fulfil the quality assessment standards, and the in vivo bioequivalence study was carried out in 17 healthy volunteers. [15]

According to Kassahun, in their study they assessed quality and physicochemical bioequivalence of five different brands of glibenclamide tablets which was marketed in Addis Ababa by in vitro and in vivo methods. The methods as described in British Pharmacopeia (2009) and United States Pharmacopeia (2007) friability, disintegration, dissolution, and assay for the content of active constituents were evaluated. The marketed brands of glibenclamide tablets complied with the specifications officially for its friability, hardness dissolution, disintegration and assay. Difference factor (f1) values were lower than 15 and similarity factor (f2) values were larger than 50 for all glibenclamide products. The in vivo studies showed that there is no significant difference in percent reduction of blood glucose level among the brands of glibenclamide and the innovator product ($p>0.05$). Depending on the in vivo results as well as in vitro dissolution studies, it suggested that the brands may be substituted with the innovator product in clinical practice [16].

PRESCRIBING PATTERN

In India, restricted studies have engrossed on diabetes care and provide an acuity into the current management and patient's profile. Approximately 50% of public with diabetes have observed poor glycaemic control, dyslipidaemia, uncontrolled hypertension and a huge percentage have diabetic vascular complications [17, 18]. Consequently, a study was conducted in diabetic patients attending a tertiary care teaching hospital in Navi Mumbai, to find the current pattern of prescribing of anti-diabetic drugs and efficacy of these drugs in sustaining adequate glycaemic control. Ethics committee Permission was obtained prior to the conduct of the study. It was a pilot study with duration of 2 months with a sample size of 100 subjects from May 10, 2010 - July 10, 2010. After obtaining informed consent ,100 diabetes patient of 18 years and above who had been receiving anti-diabetic therapy for more than 1 year was randomly designated for participation. Data (sociodemographic) along with details of anti-diabetic drug therapy, duration of treatment and life style modifications (dieting/exercise/both) was collected and recorded. Later patient's fasting and postprandial blood-glucose was measured with the help of a glucometer. The result of the study shows that out of 100 patients, 79 patients was screened passed and among the oral diabetes drugs sulphonylureas (27) was the most prescribed drugs as first line of treatment and next come the biguanides (25) [19].

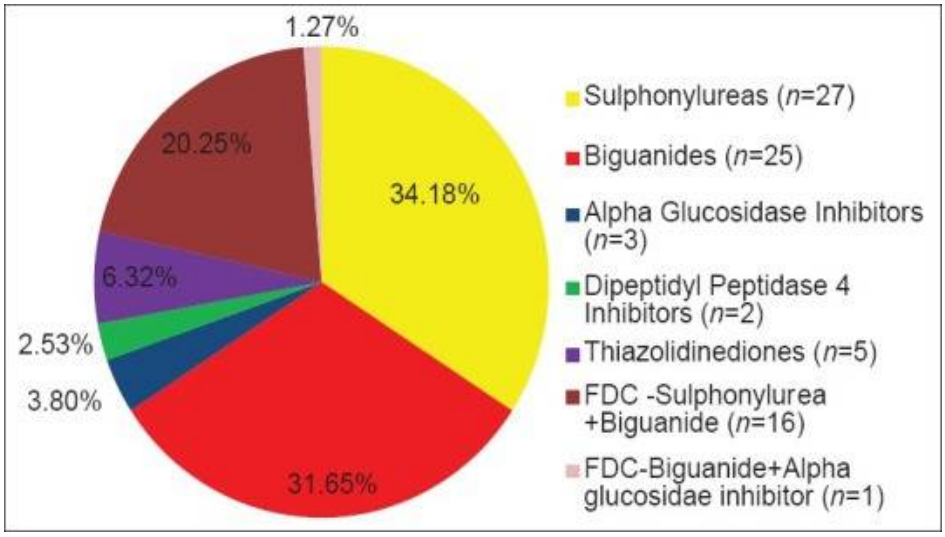

Figure 5: Prescribing frequency of different class of oral hypoglycaemic agents [32]

Another study analyzed the prescription pattern in type 2 diabetic patients, admitted to the Medicine Department of K. S. Hegde Charitable Hospital, Mangalore and the study showed that type 2 diabetes was more predominant in males than females. A total of 120 patients who satisfied the inclusion criteria were taken for the study and was performed for 5 months period time (June 2010 - October 2010) and the result of the study showed that metformin as the predominantly prescribed oral antidiabetic drug both in monotherapy and in combination therapy [20].

Bioequivalence Studies: Evaluation and Design

According to a paper, bioequivalence studies are conducted to know the bioavailability of the generic drug product to the brand-name product. Various methods (Numeric) should be looked-for to detect variation in rate and extent of absorption which are not attributed to substance inconsistency. After the bioequivalence is well established, it can be understood that both the brand-name and generic drug will show the same/similar effect [21].

Table 1: Bioequivalence Studies

The basic outline for determination of bioequivalence studies:
• The scientific queries to be answered • The nature of the reference material and the dosage form to be tested • Benefit-risk and proper attention should be paid with regard to testing in humans • The accessibility of analytical methods

The Institutional Review Board (IRB) of the organisation where the study has to be carried out must first approve the protocol of the study before the start of the study as their main responsibility is to safeguard the human subjects and their rights [22].

The bioequivalence study must be designed in a manner to easily differentiate the effects of a formulation from the effects of other drugs. When a study is to be carried out to compare two formulations then two sequence, two period crosses over design must be the choice of study design with an adequate time for washout between the two period of treatment, which is preferably equal to half-lives of the moieties to be measured or 5 times of the half-life's of the substance[23].

Human Subjects

In general, bioequivalence study is performed in healthy male and female volunteers who has been educated about their participation in the study. In a study until and unless the concern physician outlines that there is a potential benefit to the patient, disparagingly hostile patients are not recruited in the study. Intra and inter subject variable is the standard in choosing the number of volunteers to be involved in the study. The volunteers are generally made to fast overnight (i.e. 10 to 12 hours) before the first intervention of drug and may continue to fast for another couple of hours after the administration of the study drugs [24, 25].

Analytical Methods

In bioequivalence study (in-vivo), the analytical procedure used to analyse the concentration of the therapeutic or active substance, metabolite(s) of active ingredient in body fluids as well as the step to

analyse an severe effect must developed seamlessly and should be satisfactory sensitive to measure (with precision) the real absorption of the active ingredient of the drug product [26].

Reference Standard

In bioequivalence studies, one certain formulation is designated as reference(standard) drug against other preparations of the test drug to be compared. The route of drug administration to subjects should be the same in both reference and test drugs until it is mention in proposed protocol for an additional or alternative route so as to answer a pharmacokinetic query [24, 25].

The reference drug product, in bioequivalence studies is the Reference Listed Drug (RLD) which is registered in the Orange Book 'Approved Drug Products with Therapeutic Equivalence Evaluations' and the generic drug proposed is usually referred as the 'test' drug product. In general, reference listed drug (RLD) is a list of formulation which is currently advertised with a completely approved NDA with their scientific safety data and efficacy data. Typically, RLD is the original manufacturer's or innovator's brand-name drug product and is accordingly administered to the dosage mention in the labelling. In bioequivalence study with regards to in-vivo study, the test product (generic drug) must be within 5% of the reference product in its the over-all content of the active substance of the drug. Additionally, before performing the in-vivo study, in vitro comparative drug-release (drug dissolution) studies usually with specified diverse conditions are conducted for both reference and test products [24].

Extended-Release Formulations

The firmness of bioavailability study (in vivo) where a drug product of extended-release is to evaluate that if

(a) the controlled-release of the drug meets the claims made for it by the manufacturing company,

(b) The performance of the drug product's plasma steady-state is comparable to that of a currently marketed non-extended-release formulation and

(c) the profile established for the drug product stand out the incidence of any dose dumping a

(d) the formulation of the drug offers consistent performance in terms of pharmacokinetic among specific dosage units.

Regularly, solid dosage (immediate release) form is subjected to examinations for its weight, uniformity of content, hardness, friability, and test of disintegration which is commonly related with the valuation of in vivo performance is the dissolution test (11 from zaman paper).

Drug Combination Products

Generally, the tenacity of an in-vivo bioavailability study relating a combination drug product containing more than one active substance is to determine if the rate and extent of absorption of each active ingredient in the combination of drug product is corresponding to the rate and extent of absorption of each active ingredient which is simultaneously administered in preparation of separate single ingredient. To qualify as reference product in bioavailability study it has to be currently marketed two or more times single ingredient products containing on of the active ingredient in the combination products. For subject of an approved NDA, the FDA may direct that reference product be in a combination form of product for an effective scientific reason [24].

Study Design

The Food and Drug Administration, Division of Bioequivalence (Office of Generic Drugs) has proposed several drug products and have outline guidelines for performing in-vitro and in-vivo bioequivalence studies. For bioequivalence studies, healthy volunteers (male or female) should be included who had been given proper information about the study and had signed informed consent.

Times of blood sampling should be certain on the base of the commencement of the drug to be tested. Principles for bioequivalence depend on the dose frequency and the presence of food in the body of the subject. The release rate and extent of absorption must be same for the drugs under deliberation [24].

There are two experimental design of study namely Pilot and Pivotal study design.

Pilot Study

In this design, before proceeding for the full bioequivalence study it is performed on small number of human subjects and it can be assessed variability, validate analytical methodology, enhance sample collection time intervals, and deliver other information regarding the study. Bioequivalence documents from a pilot study may be accurate, provided if its design and execution are appropriate and a satisfactory number of subjects (maximum 12 subjects) completed the study [23].

Pivotal Study

Studies which provide the important evidence that help in basic decision as to the risk-benefit assessment for a specific fixed drug combination [23]

Currently for solid oral dosage forms, three basic studies are essential, including [26].

- A fasting study,
- A fed study, and/or Food Intervention Study

- A multiple-dose (steady-state) study

Fasting Study

A randomized, open-label, single-dose, two-period, two-sequence and two treatment crossover design are commonly used to determined bioequivalence studies for comparing test and reference drugs of equal strength among healthy adult subjects (inclusion of male and female) in fasting conditions. This kind of study is vital for entire immediate-release as well as modified-release dosage forms [27].

Fed Study: Food Intervention Study

Bioavailability of the drug will be interfered if the oral drug is ingested with of food. The intervention of food as well effects of food studies are performed commonly with the help of meal conditions that significantly affects gastrointestinal physiology so that systematic drug availability is extremely affected and this is the reason of withdrawing over the counter drugs and alcohol for atleast 3 days beforehand start of the study and throughout the study period [28]. The test meal is a high fat and calorie meal which may contain 2 eggs (fried in butter), 2 slices of bacon, 2 slices of bread with butter and 4 ounces of potatoes, with milk of 8 ounces. Approximately the mention meal contains calorie 150, 250 and 500- 600 from protein, fat and carbohydrate [24].

Multiple-dose Study

In certain cases, a randomized, steady-state, multiple-dose, two-treatment, two-way crossover study can be performed in healthy non-smoker adults which compare equal doses of the test as well as reference drug products [28]. In this type of studies, 3 consecutive trough concentrations (C min) on 3 incessant days should stanch to determined steady state in the human subjects. After a night fast, the subjects are administered with the last day morning dose followed by persistent fasting for a minimum of 2 hours. Similarly, blood sampling is achieved like that of the single-dose study [24].

Crossover Study Design

These design are used by several scientists in their clinical studies and in crossover design there are some considerations related (have no role in parallel-group trials) which must obtain appropriate attention for the results to be of scientific value in trial planning and analysis of data [29]. There is resembles between retrospective non-randomized crossover study and crossover study design nevertheless have differences by taking one sample of the base population-time [30].

Simply, a crossover trial in general comprises of a test and reference drug (two treatments), which are administered simultaneously in each selected subjects of the study. Informed consent is provided to subjects who qualify the selection criteria of the study [24].

A two-period study means a study which is directed on 2 different time periods by a gap of a definite time period where most of the drug is excreted from the body (about 10 half-lives). In bioequivalence study, cycle means the different number of orders in the treatment groups of the study [31]. An illustration, a two-cycle, two-period study could be calculated as follows:

Table 2: Two Period Study Design

	Period 1	Period 2
Series 1	R	T
Series 2	T	R

Where R = Reference; T = Treatment

Each subject is his/her own control, and subject-to-subject deviation is reduced in the crossover design. Additionally, deviation due to period, sequence, and treatment (formulation) are reduced, so as to avoid the subject receive the same drug product twice on the same day and order. Variation of intra-subject is generally lesser than inter subject's variableness [32]. Carryover effects of a certain drug product are lessened by changing the order or sequence in which the drug products are administered to the subject [24].

For better understanding of crossover study design, Latin square design can be adopted by comparing 3 different drugs which is given to 6 subjects at varying time periods as illustrated in table below. In this case, each subject takes each drug only 1 time, with sufficient time between treatments for the excretion of the drug [24].

Table 3: Crossover Latin-square design of 3 drug products in 6 subjects

Subject		Drug product	
	Study period 1	Study period 2	Study periods 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

Where: A is reference and B and C are the test products

Parallel Study Design

Practically, crossover design cannot be applicable for drugs which have long half-lives (more than 24 hours). In the above case, scientist can apply parallel design where separate group of subjects are administered with each treatment [19].

Replicated Crossover Study Design

A parallel design study may be replaced by a replicate crossover study which can be experiment as three or four period repetition of treatment. In this study, one treatment or both can be administered to the particular subject on two separate instances [19].This design may also be used for to estimate among subject range for both the Test and Reference drug, the determination of bioequivalence individually, and to provide an estimation of the subject-by drug product interaction variance. Mostly, FDA suggest a four-period, two-sequence, two-product design [24, 19].

Table 4: Replicated crossover study design [3]

	Period 1	**Period 2**	**Period 3**	**Period 4**
Series 1	**R**	**T**	**R**	**T**
Series 2	**T**	**R**	**T**	**R**

Where: R = Reference; T = Treatment

DATA VALUATION

Method of Data Analysis

For the evaluation of bioequivalence studies, the analytical method must be validated for accuracy, sensitivity, precision and specificity. In a bioequivalence study, it is not recommended to perform more than one analytical method, reason may be due to different values produce by different methods. detailed graphical and tabulated form for evaluation Data should be presented. The plasma drug concentration time curve should be presented for each subject and drug product [24].

Pharmacokinetic Evaluation of the Data

Cross-over study design is mostly employed in bioequivalence studies, where all the treatments are given at the same time to the subjects [14]. Including a fasting or a fed state study of single dose, the pharmacokinetic assessment of data, consist of calculation for time curve- area under the plasma concentration - time curve, that is the AUC0-t from 0 hr to the last measurable concentration, and area under the plasma concentration - time curve which is AUC0-∞ from zero to infinity to be considered as the sum of AUC0-t in addition the ratio of the last quantifiable concentration to the elimination rate constant, Tmax which is the required time to achieve maximum drug concentration in blood, and Cmax,(after the drug administration the maximum drug concentration achieved in blood) [32, 20]. Furthermore, parameters like the elimination rate constant, k, the elimination half-life, t1/2, are also estimated [24]. Pharmacokinetic analysis for multiple-dose studies includes calculation of AUC for steady state concentration, (AUC0-t), Tmax, Cmin, Cmax, and the percent fluctuation [100 x (Cmax – Cmin) / Cmin] for each subject. Appropriate statistical evaluation should be made on the pharmacokinetic parameters projected [24].

EVALUATION OF THE DATA STATISTICALLY

The retrospective analysis compares the reference and test drug from single-dose and multiple doses clinically for bioequivalence actions. Bioequivalence measures, evaluates the drug rate and extent of absorption which is represented by drug peak plasma concentration (Cmax) and area under the plasma drug concentration versus time curve (AUC), respectively [33]. So as to established bioequivalence, the data calculated must sit between the agreed limit, 80 – 125% typically, for the ratio of the product averages. To acquire data usually crossover design studies are used [24]. FDA proposed alternative method is coined as individual bioequivalence [5]. Individual bioequivalence estimates within-subject

variability for the Test and Reference products, as well as subject-by product interface and requires a replicate crossover design. At present, to set up bioequivalence of the nominated drug products an average estimate is used. The essential requirement for a bioequivalence to be established is that there should not be statistical difference between the bioavailability of the test and reference drug [24].

ANOVA: ANALYSIS OF VARIANCE

One of the statistical procedures called an analysis of Variance (ANOVA), is used to show data and the difference in data between the subject groups [24]. Many pharmacokinetic parameters like AUC, Cmax etc which results from the plasma concentration-time curve are applied to ANOVA and as a result the variance is apportioned into mechanism cause by the treatments, subjects, periods [22]. In all pharmacokinetic parameters tested, the bioequivalent product must not show any difference significantly [24].

DISCUSSION AND CONCLUSION

Therapeutic equivalence can be determined by: 1) a clinical trial showing similar efficacy and safety for test and reference drugs; 2) a clinical trial showing the same measurement of a pharmacodynamic property for both drugs; 3) a relative bioavailability test, in which pharmacokinetic curves of test and reference drugs are compared and bioequivalence is shown; 4) or in vitro tests showing pharmaceutical equivalence and the same pharmacological and technical specifications of test and reference products. considering the patient's need, drug safety, availability and the best cost-benefit ratio, is based on drug safety, efficacy and quality. However, in daily practice, the prescriber's decision is mostly influenced by drug effectiveness, following criteria that increase adherence to the treatment, such as relative drug toxicity, convenience, cost and prescriber's experience. ‘‘In addition, frequent launching of new molecules for the same therapeutic indication, together with wide publicity targeting prescribers, interferes with the decision-making process.” Similarly, the bonuses offered by the industry for over-the-counter drug sales interfere with the consumer's choice.

A manufacturer must also demonstrate that its proposed biosimilar product has no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness). This is generally demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.

Many pharmaceutical production firms are now developing new generic medication formulations for a variety of drugs. The bioequivalence analysis is important for the acceptance of generic drugs. This analysis is intended to offer a simple and quick outline of regulatory considerations for bioequivalence studies. This report addresses the main facets of bioequivalence research criteria as well as legislative requirements.

While oral hypoglycaemic agents appear to be the most widely used drug, there has been a change in the usage of insulin preparations in the treatment of Type 2 diabetes mellitus. The effectiveness of anti-diabetic drugs in maintaining optimum glycaemic management was only 41%; thus, to reduce diabetic complications, intensification of current medication therapy as well as preparing multiple drug treatments with lifestyle change is needed.

Dr. Michael Privitera, Professor of Neurology at the University of Cincinnati Medical Center voices the concern of healthcare professionals around the world: ‘Generic drugs are less expensive and everyone wants to reduce health care costs. However, our role as physicians is ‘primum non nocere’ - first do no harm. We need to be assured that the generic drugs are absolutely safe’Maintaining patients on a product with consistent bioavailability may optimize the risk-benefit balance of anticoagulation therapy.We also need to educate our patients about the use of generic drugs so that they can make an informed decision about their treatment.

FDA needs to stiffen its leash over the pharmaceutical companies making sure that spurious or counterfeit drugs do not find a footing in the drug market.

The result of Bioavailability and Bioequivalent studies enhances the area of drug interchangeability and it will also enhance option for generic drugs by the consumers which will give end result of money saving or let’s say generic drugs are pocket friendly to under privilege groups of patients. Availability of generic drugs will result in adherence to the diabetic regime since the cost of diabetic drugs is affordable and it will result is controlled diabetic patient and improve quality of life of the patients.

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