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Parameters to be Considered in A Bioequivalence Study of Drug

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Abstract: Bioequivalence is a word used to describe the biological equivalency of two proprietary medication preparations. When two medications are bioequivalent, it indicates they are expected to be the same. Pharmacokinetic studies are used to determine bioequivalence between two medications, such as a reference drug (FDA approved drug) and a potential test drug (marketed generic drug), by administering each drug to volunteers in a cross-over research (healthy individuals). To prepare a drug many aspects need to take into consideration such as in vivo and in vitro study, pharmacokinetics, pharmacodynamics and bioavailability of the drug. While designing a drug fasting, oral, crossover study of the drug needs to perform.

I. INTRODUCTION

Two pharmaceutical drugs are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities (rate and extent of bioavailability) after administration in the same molar dose are similar to such a degree that their effects, concerning both efficacy and safety, can be expected to be essentially the same. Pharmacokinetics studies are conducted to determine two products between its brand product and generic product. Ex. A receptor in the brain the brand name and the generic drug should deliver the same amount of active ingredient to the target site. The extent and drug absorption are measured under the blood and plasma concentration-time curve and maximum concentration. The bioequivalent drug provides the same therapeutic effect. Bioequivalence or pharmaceutical equivalent must be present showing that two drugs release the active ingredient into the bloodstream at the same amount, same rate, and have the same quality. Bioequivalence testing for generic drugs does not require a full clinical trial process that the name brand version had to go through.

A. Bioequivalence

Refers to the lack of a statistically significant difference in rate and the amount to which active ingredient or active moiety pharmaceutical equivalents are used. If two drugs are bioequivalent there should not be any significant difference in BA between two drugs in general bio balance is evaluated by comparing the bioavailability of the test and the reference product focuses on the release of drug sub from a drug product and subsequent absorption into systematic Circulation

BE study aims at determining whether chemically equivalent products manufactured by different companies are therapeutic equivalent BE testing required usually arises when a patent of innovator drug product expire another manufacturer may then wish to market the same formulation of the drug for malicious that are bioequivalent with that of the innovated drug is for a generic product.

B. Bioavailability

Bioavailability is the study of the rate and extent of drug absorbed in systemic circulation after administration at the site of action. Then the administered drug reaches the blood and other body fluid BA of the drug is determined through testing drug in biological fluid BA is used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation. According to the definition, when an indication Is administered intravenous rule, its BA decreases due to incomplete absorption or first-pass metabolism.

C. Pharmacokinetics

To study the mechanism of action of drugs, it's important to understand the concept of pharmacokinetics and pharmacodynamics. Generally, pharmacokinetics means what the body does to a drug. When you either take a tablet or apply a cream on your skin the first thing that takes place is absorption. So the drug has to absorb, and once it gets absorbed either through the skin or through the stomach it gets into your bloodstream and then from there it gets distributed into the fluids outside and inside the cells. Once the drug gets distributed all over the body, the body starts metabolizing it, i.e. basically modifying the drugs so that it's easy to excrete. This is done primarily by the liver, but it can also be done by other tissues. So for simplicity, the drug passes through the liver, get biotransformed and finally, gets eliminated.

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So elimination is the last step, in which the drug and its metabolites get excreted primarily in Bile urine and faeces. So when we take any drugs they follow a procedure which is, the first drug has to get absorbed. Secondly, once it reaches the systemic circulation, it gets distributed outside and inside the cells, then it starts to get metabolized and then finally, drugs get eliminated. Let's discuss them in a little bit more detail.

There are many routes by which we can administer a drug, such as parental, topical, nasal rectal, etc. But unless the drug is given IV, it must cross some membrane before it gets into the systemic circulation. So absorption of drugs can happen in four different ways. The first is passive diffusion; the second is assisted diffusion and the third through using active transportation. Finally, endocytosis is used.

1) *Passive Diffusion:* Most drugs are absorbed by passive diffusion. In passive diffusion drugs simply move from areas of high concentration to areas of lower concentration. So, if it's a water-soluble molecule, it will easily move through a channel or a pore, that's in the membrane. Now, on the other hand, if it's lipid-soluble, it will just easily pass through a membrane, without any help.
2) *Facilitated Diffusion:* So other drugs, especially larger molecules will pass with the help of carrier proteins. Just like in passive diffusion, they also move from areas of high concentration to low concentration, and the only difference is that they need a little bit of help from the carrier proteins that are in the membrane.
3) *Active Transport:* Some drugs are transported across membranes via Active energy-dependent transport. Unlike passive and facilitated diffusion, energy for this process is derived from ATP, when ATP undergoes hydrolysis to ADP, there is high energy that comes from breaking of phosphate bond.
4) *Endocytosis:* Drugs of very large size get transported via engulfment by a cell membrane, because of their large size, they wouldn't fit in a channel or a pocket of a carrier protein.

You often need to remember that absorption is not exactly that straightforward. It's a variable process dependent on pH, surface area, and blood flow. And this also leads us to the concept of bioavailability. So let me ask a question. If you take a 100-milligram oral tablet, how much of it gets absorbed in unchanged from? The answer is, it's not 100%. This is because, unlike drugs given intravenously, oral medication gets metabolized in the liver and the liver and a good portion of it gets cleared out before it reaches systemic circulation.

The cool thing is that once we administer a drug either orally or intravenously, we can then measure the plasma drug concentration over time. So, a drug given IV would start at a concentration of 100% because it bypasses the whole absorption process. However, a drug given orally would have to get absorbed first, And then some of it would get eliminated before it even reaches systemic circulation.

Once we can grab this phenomenon, we can then find areas under these curves, also known as AUC. AUC is really helpful in making comparisons between formulations and routes of administration. So finally, knowing all that bioavailability is simply AUC for the oral drug over AUC for the IV drug times 100.

$$\text{Bioavailability} = (\mathbf{AUC}_{\text{oral}} / \mathbf{AUC}_{\text{iv}}) \times 100$$

The medicine is subsequently transferred from circulation to the tissues after it has been absorbed. The distribution process is influenced by several parameters, including lipophilicity; a highly lipophilic drug would dissolve much more easily through the cell membrane than a hydrophilic molecule. Next, we have blood flow, some organs such as the brain receive more blood flow than for example skin.

So if a drug can pass through the blood-brain barrier. It will build up in the brain far faster than it will in the skin. Then there's capillary permeability; capillaries in the liver, for example, have several slit junctions through which big proteins can pass. However, there are no slit junctions in the brain, making it more difficult for a drug to pass through.

The last step in the pharmacokinetic process is the elimination, which refers to the clearing of a drug from the body mainly through the hepatic renal and biliary route.

So the total body clearance is simply the sum of individual clearance processes. Most drugs are eliminated by first-order kinetics, which means that the amount of drug eliminated over time is directly proportional to the concentration of drug in the body. Now there are a few drugs such as aspirin that are eliminated by zero-order kinetics, which means that the amount of drug eliminated is independent of drug concentration in the body. So the rate of elimination is constant.

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II. PHARMACODYNAMICS

So pharmacodynamics describes what a drug does to a body. So when a drug enters your body. It then starts interacting with cell receptors, which in turn leads to a formation of signals and this signal, through a series of different reactions, ultimately results in some biological effect. So for example, the signal can tell DNA to stop replicating cells in our body that have lots and lots of different receptors which can produce very unique responses.

The receptors that have the most therapeutic relevance can be divided into four types.

1) Ligand-gated ion channels
2) G protein-coupled receptors
3) Enzyme-linked receptors
4) Intracellular receptors.

Now we will see it in detail. Let's start with Ligand-gated ion channels. They are a large group of intrinsic transmembrane proteins that allow the passage of ions upon activation by a specific chemical. Most endogenous ligands bind to a site distinct from the ion conduction pore and binding directly causes the opening or closing of the channel. Ligands can bind extracellularly.

Next, we have the G protein-coupled receptor known as the seven-transmembrane receptor and this is because it passes through the cell membrane seven times. So these receptors are made up of three subunits: alpha, beta, and gamma, which are collectively known as G protein. The alpha subunit has GDP attached to it in its inactive form. When a ligand attaches to a receptor, the affinity for GTP rises and GTP takes the place of GDP. This in turn causes the alpha subunit to dissociate from the beta-gamma complex, and then both of these complexes, go to interact with other enzymes or proteins, which they can alter and regulate, ultimately leading to some kind of response. It's also important to remember that G protein-coupled receptors, as well as most enzyme-linked receptors, can amplify signals that they receive. So for example, just one stimulated G protein receptor can activate many other cyclists, which will result in more cyclic AMP molecules produced, and ultimately amplified response. Now let's move on to enzyme-linked receptors. These receptors, just like G protein receptors, have extracellular or binding sites where ligands typically hormone or growth factors can attach, and thus stimulate enzymatic activity inside the cell. Most enzyme-linked receptors have tyrosine kinase type, which simply means that they display kinase activity and that there is an amino acid tyrosine involved in that. So the way it works is that when a ligand binds to two of these receptors, it causes a conformational change those results in aggregation of both receptors. Once the dimer is formed, the tyrosine regions get activated and cause ATP to become ADP, which results in our phosphorylation of the receptors. Now, once each Tyrosine picks up a phosphate group. Different inactive intracellular proteins come up and attach themselves to phosphorylate tyrosine. This in turn causes a conformational change in the attached protein, ultimately leading to a cascade of activations that produce a cellular response. The last type of receptor is the intracellular receptor. Unlike the other three, this receptor is located entirely inside the cell, rather than on the cell's membrane. Therefore the ligand has to first cross the lipid membrane and then once it's inside, it can then bind to the receptor. Now the activated ligand-receptor complex can move into the nucleus, bind to DNA and regular gene expression, ultimately leading to the synthesis of specific proteins. After that, they produce a cellular response. Now let's look at an example where our signalling molecule is some kind of a drug. So as the concentration of the drug increases its pharmacologic effect also increases until we reach the point at which other receptors are occupied. If we plot this, we can determine, EC 50 from the graph, EC 50 is simply the concentration of a drug that produces 50% of the maximum effect. And it tells us how potent and efficient a drug is. One more important concept is the intrinsic activity of drugs. So, intrinsic activity refers to the ability of a drug to produce maximum effect. So if a drug binds to a receptor and can produce a maximum effect that it's comparable to the effect produced by our bodies on endogenous ligand we call it full agonists. Now, let's say about 15% of receptors show some kind of activity when there is no agonist around. This is what we call basal activity. So, again in the presence of full agonist, we will see the maximum effect. If we have an agonist, that is unable to produce maximum effect. Even if it occupies all the receptors, we call partial agonist. Lastly, if we have an agent that binds to the receptors, and instead of activating them, it stabilizes receptors in the inactive form, we called inverse agonist, and this is because it simply eliminates basal activity. On the other side of the spectrum, we have an antagonist, which refers to a ligand that can bind the receptor, and block it, that's reducing agonist activity. So if we have both agonists and antagonists that can bind to the same side of the receptor they will compete for that side. Therefore, antagonists bind and prevent agonists from binding. It's called competitive antagonists. The last important concept in pharmacodynamics is the therapeutic index. Our bodies are very complex; therefore not everyone will experience the same effect from the same dose of a drug. This is why we came up with the therapeutic index as it helps us to measure the relative safety of a drug for a particular treatment so the therapeutic index is simply the ratio of the dose of a drug that produces toxicity in 50% of the population to the dose of a drug that produces an effective response in 50% of the population.

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III. BIOEQUIVALENCE STUDIES

There are two types of Bioequivalence studies

A. *In Vivo Studies*

These are the studies in which the effects of biological entities on whole organisms or plants are studied. It is preferred over the in vitro studies because it gives more overall understanding and the overall effect of the experiment on a living object.

B. *In vivo Bioequivalence Studies*

In vivo Bioequivalence testing must be carried out in such a manner that it should be most accurate, sensitive and it can be reproducible. The process of in vivo bioequivalence testing is conducted in the following sequence, as it starts with Fundamental Bioequivalence Assumption followed by conducting a bioequivalence study under a valid study design, appropriate statistical methods for assessment of average bioequivalence, and regulatory submission, review, and at the end approval. The concentration of active material or therapeutic margin or its representative metabolites in the blood, plasma, serum or other body fluids or appropriate tissue parts of targeted species is measured as a function of time in the in vivo Bioequivalence studies. Sufficient drug concentration must be achieved to allow for the determination of product concentration versus time profile in the blood or other biological fluid. In vivo bioequivalence data depends upon an assumption that the measured concentrations of active substances have meaning concerning the objective of the trial and the planned label claim. The appropriate acute pharmacological effect of the active substance or therapeutic margin or its metabolites is measured as a function of time in the targeted species used in the in vivo Bioequivalence testing. It is useful for understanding drug-related responses. The pharmacological end-points can be the most appropriate approach for the demonstration of bioequivalence, in the products planned for local effects.

The following sequence of criteria is useful and important in assessing the necessity for in vivo Bioequivalence studies

1) Oral immediate-release products with systemic action.
2) Drugs Indicated for serious conditions requiring an assured response.
3) Drugs having narrowed therapeutic margins.
4) Pharmacokinetics is complicated by absorption < 70%.
5) Unfavourable physio-chemical properties. Eg slow solubility, instability.

C. *In Vitro Studies*

In vitro studies are done with microorganisms, cells or biological molecules in the labware like test tubes, flasks and the Petri dishes. These studies can give simpler, specific and detailed analysis, replacing studies on the whole body.

D. *In vitro Bioequivalence Studies*

According to the FDA guidelines, for the assessment of in vitro Bioequivalence there requires seven in-vitro testings. These In vitro tests include testing of (i) single actuation content through Container life, (ii) droplet size distribution by laser diffraction, (iii) Drug in small particles/droplets, or particle/droplet size distribution by Cascade impactor, (iv) Drug particle size distribution by microscopy, (v) Spray pattern, (vi) plume geometry, and (vii) priming and re-priming.

E. *Need Bioequivalence*

Bioequivalence indicates biochemical similarity between two drugs having the same active ingredients and shows a similar effect on the patient. We can say the drugs are bioequivalence of each other only if they show the same effect at the site of physiological activity and having identically active ingredients.

1) Bioequivalence studies comparing the bioavailability of brand name drugs and generic drugs.
2) It gives clinical investigations for assessing the therapeutic equivalence of drugs.
3) BE studies giving methods and conditions for identifying the relevant difference between drug products.
4) In the pharmaceutical industry BE studies are considered an important event in the development of pharmaceutical preparations.
5) After the administration of the tested drug BE studies were performed to monitoring pharmacokinetics and pharmacodynamics parameter.
6) BE studies evaluate the pharmaceutical equivalent of pharmaceutical alternative of tested drug.
7) The importance of bioequivalence studies is increasing due to the large growth in production and consumption of the generic product.

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F. Bioavailability of Novel Method

Bioavailability consists of many ways like assumption also experimentally verified. It was assumed that the same fraction of the absorbed compound from different preparations is excreted unchanged in the urine. Hence the following same dose about urine recovery. Pharmacokinetic methods of assessing bioavailability from blood plasma concentrations or urinary excretion data were summarized by Wagner. This is based on consist of plasma concentration compared with the product of plasma clearance and the total area under the curve (AUC). If one assumes to be constant for a given subject from one test dose to another, then the ratio of **(AUC),** is a measure of relative absorption. The nature of such an adjustment depends on one's ability to estimate the terminal plasma.

Table. 1- Simulated Plasma Concentration and Urinary Excretion Data following Single 500 mg. Intervenous and oral Doses of a Drug to the same subject on three separate occasions.

Treatment	Plasma Concentration, mcg./ml., in Minutes											
	5	10	20	30	40	60	120	180	240	300	360	720
Intravenous	17.99	15.12	11.21	8.78	7.14	5.05	(2.09)	(0.89)	(0.38)	0.16	0.07	—
Oral No. 1	—	—	1.43	—	2.06	2.32	(2.22)	(1.69)	(1.17)	0.77	0.49	0.02
Oral No. 2	—	—	4.50	—	5.42	5.15	(3.15)	(1.65)	(0.82)	0.40	0.20	0
	Urinary Recovery, mg., in Hours											
	−1–0	0–1	1–2		2–3	3–4		4–6	6–12	12–24	0–24	
Intravenous	0	171.97	56.30		(23.77)	(10.14)		6.18	1.37	0	(269.73)	
Oral No. 1	0	21.45	31.25		(26.27)	(19.02)		21.08	12.64	0.59	(132.30)	
Oral No. 2	0	50.81	48.08		(26.91)	(13.74)		10.12	3.10	0.20	(152.96)	

In pharmacokinetic terms, the assumptions are that component rates of total elimination are individually constant or that the ratio of the rate of urinary excretion to the overall rate of elimination of that which is absorbed is constant. Intrasubject variations in the rate of urinary excretion are manifested as changes in the slopes of the amounts remaining to be excreted **versus** time plots. Compensations are subject to the same considerations as with plasma ***fl,*** and are, therefore, also model-dependent. Depending on the biological disposition of the drug,

Bioavailability studies are designed to utilize one or more of these methods. Such studies should include means for testing some of the assumptions. Where it is safe and experimentally feasible, it **is** generally desirable to include at least one intravenous dose as a reference of maximum bioavailability. The purpose of this report is to describe a different experimental strategy that utilizes plasma concentration and urinary excretion data together to permit greater flexibility in the design of bioavailability protocols.

G. Bioequivalence Novel Method

Bioequivalence is generally the concept of comparison of two drug products. As consider classical bioequivalence approach consist two drugs product under evaluation(T) versus innovator product(R). Consider if calculated bioequivalent at 90% confidence interval of the ratio of a log transfer exposure measure at AUC or Cmax. But here we calculated the difference of logarithmic transformed that is MU T and MU R. MU T means a value of the pharmacokinetic parameters for T) and MU R means a value of the pharmacokinetic parameters for R. The testing approach of BE is based on constant BE limits (below).

BE is mathematically expressed with the equation as follow:

$$-BEL_0 \le \mu_T - \mu_R \le BEL_0 \quad \ldots (1)$$

where BEL0 is usually set equal to ln(1.25) as shown in fig.1 Assuming the classic two-period, two treatment, cross over with the equal number of subjects in each sequence so the upper and lower limit of 90% CI value is given by equation 2 :

$$\text{Upper, Lower limits of the 90\% CI} = \exp\left((m_T - m_R) \pm t_{0.05,N-2}\sqrt{s^2 2/N}\right) \quad \ldots (2)$$

Where mT and Mr are the estimated log transfer means it measures BA for T and R products respectively. The term of s means the square error of ANOVA(Analysis of variance) which reflect. Intra subject variability (omega W square),t is the t-student statistic with N-2 degrees of freedom and N is the number of subjects participating in the BE study. The use of the average BE approach in the case of a toxic drug or high variable drug with low variability and narrow therapeutic range. As seen in fig.1 we realize that average BE allows the large differences. The latter constitutes a potential problem of switchability for multisource formulations, each declared bioequivalent to the same R product.

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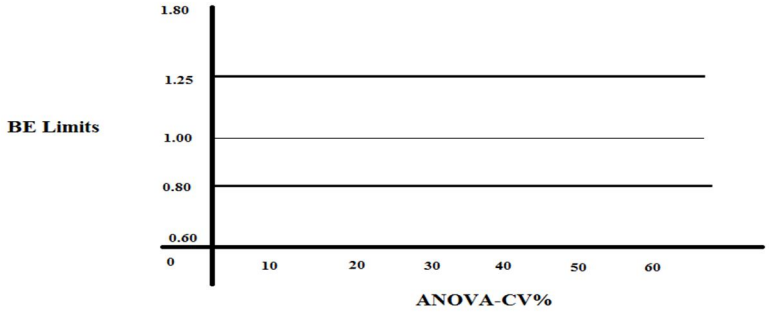


Fig. 1BE limits as a function of within-subject variability (ANOVA-CV%) for the classic (0.80- 1.25) limits

IV. CASE REPORT ON BIOEQUIVALENCE STUDY OF FAVIPIRAVIR TABLET IN HEALTHY MALE SUBJECTS

Generally, Favipiravir was being used in outbreaks of re-emerging influenza viral infection where other antiviral agents are not so effective. Favipiravir is metabolized into favipiravir ribosyl triphosphate by an intracellular enzyme. The favipiravir uses selective inhibition of RNA polymerase enzymes in the influenza virus leading to antiviral activity. Favipiravir is effective against many types of Influenza viruses. According to a study, favipiravir is active against a wide range of other RNA viruses in vitro and in vivo. In vitro studies have no emergence of resistance towards favipiravir. It is also utilized in the treatment of coronavirus. There are several clinical trials on potential antiviral therapies happening. The therapies are often divided into two categories counting on their target. One is acting on the coronavirus directly, or by blocking the entry of the virus into human cells. The second one is designed to modulate the human immune system by boosting the innate response. The bioequivalence study is required for generic orally administered Favipiravir products. This case study aims to compare the pharmacokinetic properties of a generic formulation with the reference to the product.

A. Method of Study

A two-period study was conducted on 30 healthy, adult, male, human subjects under fasting conditions. This study was conducted at FARMAGEN-Good Clinical Practice Center, Turkey. This clinical study lasts till 9 days, which includes screening, isolation, and final examination. The standard laboratory examinations of blood and urine were examined regularly. Also, Covid-19 PCR tests were applied to the volunteers before the isolation period. Depending on the suitability of the volunteers' clinical examination, an isolation period was provided for 4 nights in single rooms reserved. And due to the pandemic situation, all volunteers were placed isolated from each other. A total of 30 volunteers were participating from which 29 volunteers completed their clinical trials

It was found that Favipiravir is one of the best drugs in Covid-19 treatment. The ANOVA results showed that treatment, sequence, period, and subject within sequence had no statistically significant effect. CVs were found as 29.053% and 6.668%. The mean ratios were found as 105.55% and 96.84% for Cmax and AUC0-test, respectively. There were five sampling points in the first hour. All extrapolated areas were found below 20% which could be interpreted as the study had adequate sample collection times. In conclusion, since the 90% CIs for the test/reference geometric mean ratios for C_{max} and AUC0-last of Favipiravir is contained within the acceptance limits preset in the Clinical Study Protocol, 80.00-125.00%, according to the applied bioequivalence study, it is concluded that test and reference Favipiravir products are bioequivalent under fasting conditions and test product can be licensed under the requirements of regulatory authorities.

B. Study Design

The FDA division of the bioequivalence study office of generic drugs gives guidelines for performing in-vivo bioequivalence and in-vitro dissolution studies. All these guidelines are given by United States pharmacopoeia NF.

Bioequivalence studies include, in the study should be both male and female volunteers and who signed the agreement. Sampling time should be chosen based on the drug to be tested for bioequivalence. Norms for bioequivalence depend on the dose frequency and the presence of food in the body of the subject. For the drug, under consideration, the proportion of absorption and release rate should be the same. Because of the following points, the design of an in vivo bioavailability study is determined.

1) The nature of the reference drug
2) The availability of analytical methods
3) Benefits risk ratio consideration with testing in humans.
4) What is the scientific question to be answered

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V. STUDY CONDITION

Standardization of the study is important in bioequivalence such as environment, exercise, sampling schedule, fluid intake, diet, post-dosing postures, etc. it also requires that all variability factors, the subject should avoid coffee, tea, smoking, drinking alcohol, xanthine containing foods and beverages, fruit juices during the study and at least 48 hours before commencement.

Guidelines provided by FDA for the performance of in vitro and in vivo bioequivalence studies which include solid oral dosage form. This would require different studies as follows

1) A fasting study
2) A food intervention study design(fed study)
3) A multiple-dose study
4) Parallel study design
5) Replicated crossover study design

A. Fasting Study

This study is needed for all modified release and immediate-release oral dosage forms. Bioequivalence studies are usually evaluated by a single dose, two periods, to treatment, open-label, two sequence randomized crossover design comparing equal doses of the test and reference products in fasted, healthy, adult subjects. This study, including both male and female subjects. Blood sampling is performed just before (zero time) the dose and at a particular period of the dose to obtain an adequate description of the plasma drug concentration-time profile.

Usually, a single dose study should be in the fasting state at least 10 hours before drug administration and should continue to fast for up to four hours after dosing. For multiple-dose fasting state studies, when an evening dose must be given, two hours of fasting before and after a dose is necessary.

B. Food Intervention Study Design (fed study)

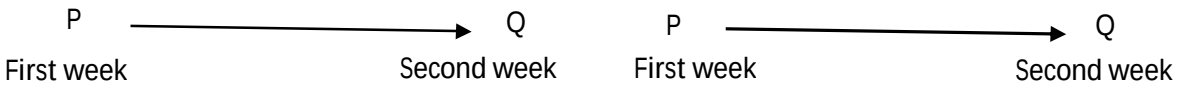
Administration of food with an oral drug product may impose the bioavailability of the drug. When it is suggested the drug is given with food. Along with the fasting study, fed state study needs to be carried out using meal conditions. That greatly affects GI physiology such that systemic drug availability is maximally affected. So, it is necessary to avoid counter drugs and alcohol three days before the start of the experiment and during the experiment. Studies in fed states require the utilization of high fat and high-calorie breakfast/meal before dosing. Such meals are designed to provide 950 to 1000 Kcals. Among these 50% of these calories must come from fat, 15 to 20 % from proteins and remaining from carbohydrates. A typical meal may consist of two strips of milk and two eggs fried in butter.

C. Multiple-dose Study

In a few cases, multiple-dose, steady-state, two treatments, randomized, two-way crossover studies comparing equal doses of the test and reference products may be carried out in healthy non-smoker adult healthy subjects. For these studies, three consecutive trough concentrations (Cmax) on three successive days should be determined to ascertain that the subjects are at a steady-state. The last morning dose is given to the subject after an overnight fast, with continual fasting for at least 2 hours following dose administration. Blood sampling is carried out the same as to the single dose.

D. Crossover Study Design

The crossover study is a very popular and often desirable, design clinical trial. Many researchers perform crossover study designs. In these designs, two treatments are compared, with each patient or subject taking each treatment in turn. The treatment is performed in a randomized pattern; i.e P is followed by Q or Q is followed by A, where P and Q are the two treatments. These treatments were carried out on two occasions, often called visits, periods or legs. In a particular situation, the treatments are not separated by time e.g, in two visits or periods. The crossover study design includes both reference drugs and test drugs which are consecutively administered in a subject. For instance, comparing the effects of current products, location of smearing on the body may serve as visits or periods. Products may be applied to each of the two arms, right and left. subjects will be differentiated into two groups, (1) those with Product P employed on the left arm and Product Q on the right arm, and (2) those with Product Q employed on the left arm and Product P on the right arm.



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The basic crossover or simple reversal trial can be defined as one in which two treatments (P and Q) are studied, and the animal cow experimental unit receives both trials in either of the sequences P, Q or Q, P. The crossover design method is a type of Latin square. In these studies, the number of trials is equal to the number of subjects. Each subject receives each drug product only once, with a specified time between medications for the knockout of the drug. The crossover study design can be understood by comparing three different drug products given to six volunteers at discrete periods as shown in table 1.

Table 1. Latin Square crossover design for bioequivalence study 6 volunteers and 3 products

Volunteers	Drug product		
	Study period 1	Study period 2	Study period 3
1	P	Q	R
2	Q	R	P
3	R	P	Q
4	P	R	Q
5	R	Q	P
6	Q	P	R

(Where P is reference and Q is test drug products)

The crossover order of treatment is included in the experiment in a balanced way. The total result is N*N array (where N is several volunteers or treatments)of N letters such that a given letter appears only once in a given row or column. This is most easily shown pictorially. A Latin square for four subjects taking four drugs is shown in table 2. For randomizations of treatments in Latin squares, For the comparison of two formulations, a 2 X 2 Latin square as in table 1 (N = 2) consists of two patients each taking two formulations (A and B) on two different occasions in two "orders".

Table 2: 4 X 4 Latin Square: four volunteers take four drugs.

Order in which drugs are taken				
volunteers	Study period 1	Study period 2	Study period 3	Study period 4
1	A	B	C	D
2	B	C	D	A
3	C	D	A	B
4	D	A	B	C

E. Parallel Study Design

Parallel design can be carried out for drugs having an extremely long half-life. In which treatment is administered to a distinct group of volunteers. In the parallel study design, even several subjects in two formulations either tests or standards are administered to groups of volunteers. Table 1 group 1 receiving formulation A and after some time again formulation B. Group 2 receives formulation B and again sometime Formulation B. Here, A can be a test product and B can be a reference product. The disadvantage is of parallel study design is inter-subject variation or carryover effect.

Table 3. Parallel study design

groups	formulation	
Group 1	A	A
Group 2	B	B

F. Acceptance Criteria

1) If the analysis doesn't show a difference in effects then it clearly shows that it could not have been proved.
2) If the analysis shows a significant difference in treatment that is not relevant.
3) A decision in favour of bioequivalence is taken if the interval of confidence has contained a limit of acceptance. These limits are fixed. 70%,130% for Cmax of doxycycline.
4) Sometimes specific substances should be larger because most BE studies will not possible due to variability in data.
5) There is still confusion limits of acceptance should be 90%, 95% in a confidence interval. The limit of acceptance is stated as a reference value (80%,120%).

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6) There is one more argument in favour of analysis after logarithmic, If data is analyzed the limit of acceptance should be 20% of reference mean. On the other hand, if the data analyzed is geometrical, the limit of acceptance should be 80%,120%.

7) There is also one-sided limits (80%,120%) for certain antibiotics.

8) We should keep in mind that, where confidence interval is not fully contained within a region of acceptance but overlaps it, there is no conclusion for bioequivalence is possible.

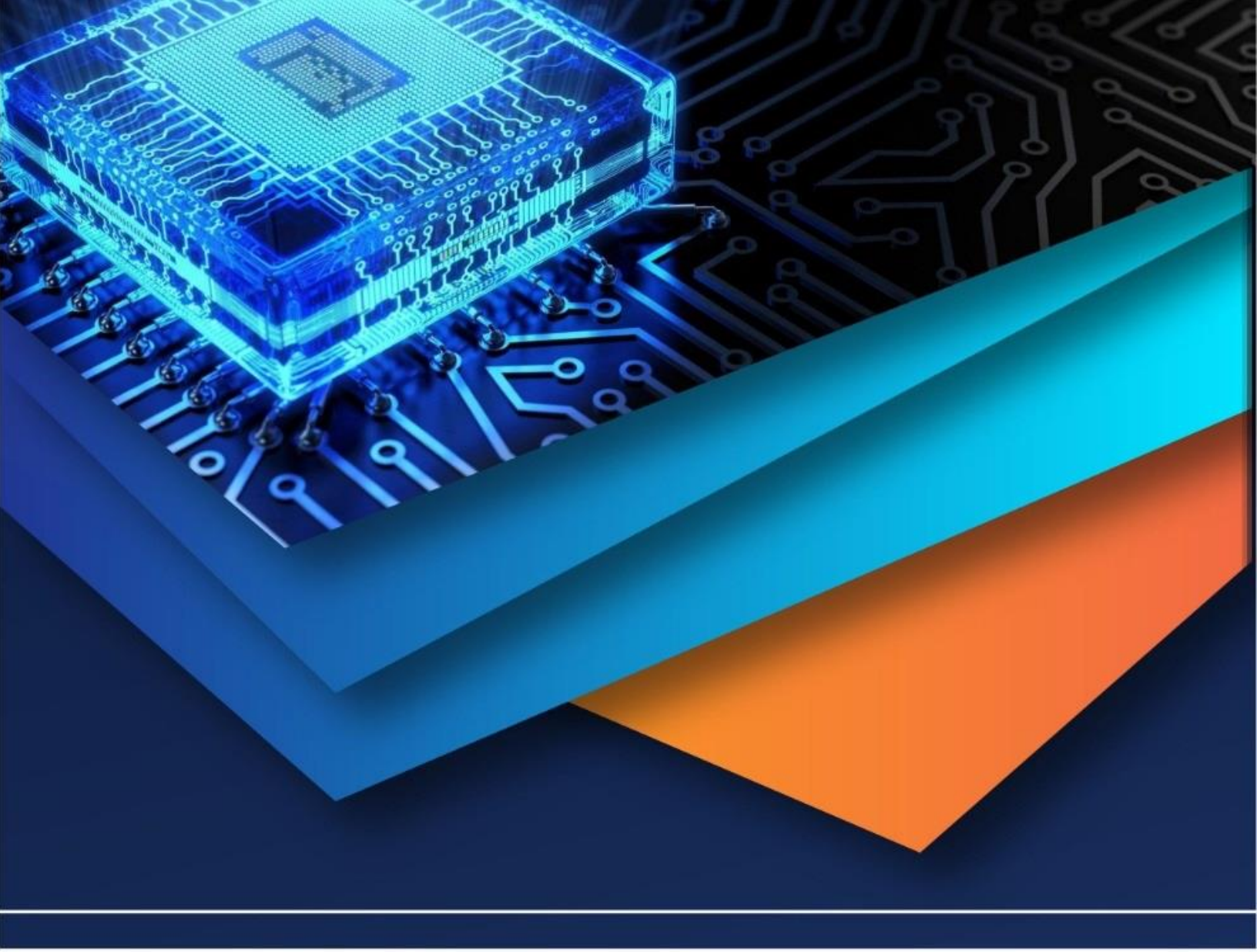
VI. CONCLUSION

Many pharmaceutical manufacturing companies are now developing alternative generic medicine products for a variety of drugs. The bioequivalence study is essential for the approval of generic drugs. This review is intended to provide the parameter which needs to take into consideration in the designing of the drug and a simple and rapid overview of regulatory considerations for bioequivalence investigations and design.

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