International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.5, No.4, pp 1711-1721, Oct-Dec 2013

A Review Article on Bioavailability and Bioequivalence Studies

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Abstract: Bioequivalence is a term in pharmacokinetics used to assess the expected in vivo biological equivalence of two proprietary preparations of a drug. If two drugs are bioequivalent it means that they would be expected to be, for all intents and purposes, the same.

In determining bioequivalence between two drugs such as a reference drug (Brand) and potential to be test drug (marketed generic drug), pharmacokinetic studies are conducted whereby, each of the drugs are administered in a cross over study to volunteers subjects (healthy individuals). Serum/plasma are obtained at regular intervals and assayed for parent drug (metabolites) concentration. Blood concentration levels are neither feasible or possible to compare the two drugs, then pharmacodynamic endpoints rather than pharmacokinetic end points are used for comparison. For a pharmacokinetic comparison, the plasma concentration data are used to assess key pharmacokinetic parameters such as area under the curve (AUC), peak concentration (Cmax), time to peak concentration (Tmax), and absorption lag time (tlag). Testing should be conducted at several different doses, especially when the drug displays non-linear pharmacokinetics.

If 90% Confidence interval for the ratio of the geometric least square means of natural log transformed Cmax, AUC0-t and AUC0-inf of Test and Reference drugs are within 80.00% to 125.00%, then bioequivalence will be establish.

Key words: Bioavailability and Bioequivalence studies.

Introduction

Bioequivalence is a term in pharmacokinetics used to assess the expected in vivo biological equivalence of two proprietary preparations of a drug. If two products are said to be bioequivalent it means that they would be expected to be, for all intents and purposes, the same.

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substances, in the same dosage form, for the same route of administration and meeting the same or comparable standards.[1]

The absence of a significant difference in the rate and extent to which the active ingredient in pharmaceutical equivalents becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[2]

Ensuring uniformity in standards of quality, efficacy and safety of pharmaceutical products is the fundamental responsibility of central drugs standard control organization (CDSCO). Reasonable assurance has to be provided that various products, containing active ingredients, marketed by different licensees, are clinically equivalent and interchangeable.

Bioavailability and bioequivalence data is therefore required to be furnished with applications for new drugs, as required under schedule Y, depending on the type of application being submitted.

Both bioavailability and bioequivalence focus on the release of a drug substance from its dosage form and subsequent absorption in to the systemic circulation.

Bioavailability can be generally documented by a systemic exposure profile obtained by measuring drug concentration in the systemic circulation over time. The systemic exposure profile determined during clinical trials in the early drug development can serve as a benchmark for subsequent bioequivalence studies.

Bioequivalence studies should be conducted for the comparison of two medicinal products containing the same active substance. Two products marketed by different licensees, containing same active ingredients, must be shown to be therapeutically equivalent to one another in order to be considered interchangeable. Several test methods are available to assess equivalence, including:

- Comparative bioavailability (bioequivalence) studies, in which the active drug substance is measured in an accessible biological fluid such as plasma, blood.
- Comparative clinical trials
- Comparative pharmacodynamic studies in humans[3]

Target Of The Guidelines

Bioavailability and Bioequivalence studies are required by regulations to ensure therapeutic equivalence between a pharmaceutically equivalent test drug and a reference drug.

When types of studies required in bioequivalence studies

In vivo studies

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

- Oral immediate release drug formulations with systemic action when one or more of the following:
- Indicated for serious conditions requiring assured therapeutic response
- Narrow therapeutic window, steep dose-response curve
- Pharmacokinetics complicated by variable or incomplete absorption or absorption window, nonlinear pharmacokinetics, pre-systemic elimination
- Unfavourable physicochemical properties, e.g., low solubility, instability, meta-stable modifications, poor permeability, etc.
- Documented evidence for bioavailability problems related to the drug or drugs of similar chemical structure or formulations,
- Where a high ratio of excipients to active ingredients exists
- Non oral and non parenteral drug formulations design to act by systemic absorption.

- Sustained release drug formulations design to act by systemic absorption
- Fixed dose combination products with systemic action
- Non solution pharmaceutical products which are for non systemic use and are intended to act without systemic absorption. In these cases, the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are requiring to prove equivalence. There is a need for drug concentration measurements in order to assess unintended partial absorption.

Bioequivalence documentation is also needed to establish links between:

- Early and late clinical trial formulations
- Formulations used in clinical trials and stability studies
- Clinical trial formulations and to be marketed drug products

In each comparison, the new formulation or new method of manufacture shall be the test drug and the prior formulation shall be the reference drug.

When no need of bioequivalence studies

In the following formulations and circumstances, bioequivalence between a test drug and a reference drug may be considered self evident with no further requirement for documentation:

- When a gas is in the form of test drug
- When test drugs are to be administered parenterally (such as subcutaneous, intramuscular, intravenous etc) as aqueous solution and contain the same active ingredients in the same concentration and the same excipients in comparable concentrations
- When the test drug is in the form of solution for oral use, and contains the active ingredients in the same, and does not contain an excipient that is known to affect gastro-intestinal absorption of the active ingredients.
- When the test drug is in the form of an ophthalmic or topical product prepared as aqueous solution and contains the same active ingredients in the same concentrations and essentially the same excipients in comparable concentrations
- When the test drug is in the form of powder for reconstitution as a solution and the solution meets either above second and third points
- When a test drug is in the form of an inhalation product or a nasal spray, tested to be administered with or without the same device as the reference drug, prepared as aqueous solutions, and contain the same active ingredients in the same concentration and essentially the same excipients in comparable concentrations.

Design And Conduct Of Pharmacokinetic Studies

Study design

According to following points the design of an in vivo bioavailability study is determined:

- The nature of the reference drug and the dosage form to be tested
- Benefit risk ratio considerations in regard to testing in humans
- The availability of analytical methods
- What is the scientific questions to be answered

Alternative study designs include the parallel design for very long half life substances with highly variable disposition.

Single dose studies generally suffice. However situations as described below may demand a steady state study design:

- Some modified release drugs
- Where problems of sensitivity preclude sufficiently precise plasma concentration measurements after single dose administration
- Dose or time dependant pharmacokinetics
- If intra individual variability in the plasma concentration or disposition precludes the possibility of demonstrating bioequivalence in a reasonably sized single dose study and this variability is reduced at steady state

Selection of the number of subjects

The number of subjects required for a study should be statistically significant and is determined by the following considerations:

- The level of significant should be 0.05
- The error variance associated with the primary characteristics to be studied as estimated from a pilot experiment, from previous studies
- The expected deviation from the reference drug compatible with bioequivalence
- The required power, normally >80% to detect the maximum allowable difference in primary characteristics to be studied

Selection criteria for subjects

The studies should be normally performed on healthy adult volunteers with the aim to minimize variability and permit detection of differences between the study drugs. Subjects may be males or females; however the choice of gender should be consistent with usage and safety criteria. To minimize intra and inter individual variation subjects should be standardized as much as possible and acceptable.

Genetic Phenotyping

Phenotyping and genotyping of subjects should be considered for exploratory bioavailability studies and all studies using parallel group design. It may also be considered in crossover studies for safety.

Study Conditions

Standardisation of the study environment, diet, fluid intake, post dosing postures, exercise, sampling schedules etc. is important in all studies. Compliance to these standardizations should be stated in the protocol and reported at the end of the study, in order to reassure that all variability factors involved, except that of the products being tested, have be minimized. Unless the study design requires, subjects should abstain from smoking, drinking alcohol, coffee, tea, xanthine containing foods and beverages and fruit juices during the study and at least 48 hours before its commencement.

Selection of blood sampling schedules

The blood sampling period in single dose trials of an immediate release product should extend to at least three elimination half lives. Sampling should be continued for a sufficient period to ensure that the area extrapolated from the time of the last measured concentration to infinite time is only a small percentage (less than 20%) of the total AUC. The use of a truncated AUC is undesirable except in certain circumstances such as in the

presence of entero-hepatic recycling where the terminal elimination rate constant cannot be calculated accurately.

There should be at least three sampling points during the absorption phase, three to four at the projected Tmax and four points during the elimination phase. The number of points used to calculate the terminal elimination rate constant should be preferably determined by eye from a semi logarithmic plot.

Intervals between successive sampling points used to calculate the terminal elimination rate constant should, in general, not be longer than the half life of the study drug.

Where urinary excretion is measured in a single dose study it is necessary to collect urine for seven or more half lives.

Fasting and fed state considerations

Generally, a single dose study should be conducted after an overnight fast (at least 10 hours), with subsequent fast of 4 hours following dosing. For multiple dose fasting state studies, when an evening dose must be given, two hours of fasting before and after the dose is considered acceptable.

However, when it is recommended that the study drug be given with food (as would be in routine clinical practice), or where the dosage form is a modified release product, fed state studies need to be carried out in addition to the fasting state studies.

Fed state studies are also required when fasting state studies make assessment of Cmax and Tmax difficult.

Studies in the fed state require the consumption of a high fat breakfast before dosing. Such a breakfast must be designed to provide 950 to 1000 KCals. At least 50% of these calories must come from fat, 15 to 20% from proteins and the rest from carbohydrates. The vast ethnic and cultural variations of the Indian sub continent preclude the recommendation of any single standard high fat breakfast. Protocol should specify the suitable and appropriate diet. The high fat breakfast must be consumed approximately 15 minutes before dosing.

Steady state studies

In following cases an additional “steady state study” is considered appropriate:

- Where the drug has a long terminal elimination half life and blood concentrations after a single dose can not be followed for a sufficient time.
- Where assay sensitivity is inadequate to follow the terminal elimination phase for an adequate period of time.
- For drugs, which are so toxic that ethically they should only be administered to patients for whom they are a necessary part of therapy, but where multiple dose therapy is required, e.g. cytotoxics.
- For modified release products where it is necessary to assess the fluctuation in plasma concentration over a dosage interval at steady state.
- Where the drug is likely to accumulate in the body.
- For drugs that exhibit non linear (i.e., dose or time dependent) pharmacokinetics.
- For combination products where the ratio of plasma concentration of the individual drugs is important.
- For those drug which induce their own metabolism
- For enteric coated preparations where the coating is innovative.

Characteristics To Be Investigated During Bioequivalence Studies

In most cases evaluation of bioavailability and bioequivalence will be based upon the measured concentrations of the active drug substances in the biological matrix. In some situations, the measurements of an active or inactive metabolite may be necessary. These situations include:

- Where the concentrations of the drugs may be too low to accurately measure in the biological matrix
- Limitations of the analytical method
- Unstable drugs
- Drugs with a very short half life.

Racemates should be measured using an achiral assay method. Measurement of individual enantiomers in bioequivalence studies is recommended where all of the following criteria are met:

- The enantiomers exhibit different pharmacodynamic characteristics
- The enantiomers exhibit different pharmacokinetic characteristics
- Primary efficacy/safety activity resides with the minor enantiomer
- Non linear absorption is present for at least one of the enantiomers

The plasma time concentration curve is mostly used to assess the rate and extent of absorption of the study drug. These include pharmacokinetic parameters such as the C_{max}, $T_{max,}$ AUC_{0-t} and $AUC_{0-\infty.}$

For studies in the steady state AUC0-τ, $C_{max,}$ $C_{min,}$ and degree of fluctuation should be calculated.[4]

Bioavailability/Bioequivalence Testing

In determining bioequivalence, for example, between two drugs such as a commercially available brand drug and a potential to be marketed generic product, pharmacokinetic studies are conducted whereby each of the preparations are administered in a cross over study to volunteer subjects, generally healthy individuals but occasionally in patients, serum/plasma samples are obtained at regular intervals and assayed for parent drug (or occasionally metabolite) concentration. Occasionally, blood concentration levels are neither feasible nor possible to compare two drugs (e.g. inhaled corticosteroids), then pharmacodynamics endpoints rather than pharmacokinetic endpoints are used for comparison. For a pharmacokinetic comparison, the plasma concentration data are used to assess key pharmacokinetic parameters such as area under the curve (AUC), peak concentration (C_{max}), time to peak concentration (T_{max}), and absorption lag time (tlag). Testing should be conducted at several different doses, especially when the drug displays non linear pharmacokinetics.

In addition to a data from bioequivalence studies, other data may need to be submitted to meet regulatory requirements for bioequivalence such evidence may include:

- Analytical method validation
- In vitro-in vivo correlation studies[5]

Criteria for bioequivalence

To establish bioequivalence, the calculated 90% confidence interval for AUC and Cmax should fall within the bioequivalence range, usually 80.00-125.00%. This is equivalent to the rejection of two one sided-t tests with the null hypothesis of non bioequivalence at 5% level of significance. The non-parametric 90% confidence interval for Tmax should lie within a clinically acceptable range.

Tighter limits for permissible differences in bioavailability may be required for drug that have:

- A narrow therapeutic index

- A serious, dose-related toxicity
- A steep dose/effect curve
- A non linear pharmacokinetics within the therapeutic dose range

A wider acceptance range may be acceptable if it is based on sound clinical justification.

In case of supra-bioavailability, a reformulation followed by a fresh bioequivalence study will be necessary. Otherwise, clinical trial data on new formulation will be required to support the application, especially dosage recommendations. Such formulations are usually not be accepted as therapeutically equivalent to the existing reference drug. The name of the new drug should preclude confusion with the earlier approved drug.[3, 4]

Regulatory Definitions In Study

Australia

In Australia, the Therapeutics Goods Administration (TGA) considers preparations to be bioequivalent if the 90% confidence intervals (90% CI) of the rate ratios, between the two preparations, of C_{max} and AUC lie in the range 0.80-1.25. T_{max} should also be similar between the products.

There are tighter requirements for drugs with a narrow therapeutic index and/or saturable metabolism thus no generic drugs exist on the Australian market for digoxin or phenytoin for instance.[1]

Europe

According to regulations applicable in the European Economic Area[6] two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same. This is considered demonstrated if the 90% confidence intervals (90% CI) of the ratios for AUC_{0-t} and C_{max} between the two preparations lie in the range 80.00 – 125.00%.

United States

The FDA considers two products bioequivalent if the 90% CI of the relative mean C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of the test (e.g. generic formulation) to reference (e.g. innovator brand formulation) should be within 80.00% to 125.00% in the fasting state. Although there are a few exceptions, generally a bioequivalent comparison of Test to Reference formulations also requires administration after an appropriate meal at a specified time before taking the drug, a so-called "fed" or "food-effect" study. A food-effect study requires the same statistical evaluation as the fasting study, described above.[2]

Crossover Design

As recommended by the US FDA (1992),[7] in most bioequivalence studies, a “test” drug is compared with the standard “reference” drug, in a group of normal, healthy subjects (18- 55 yr), each of whom receive both the treatments alternately, in a crossover fashion (two-period, two-treatment crossover design), with the two phases of treatment separated by a “washout period” of generally a week’s duration, but may be longer (a minimum time equivalent to 5half-lives) if the elimination half-life of the drug is very long.

The treatment is assigned to each subject, randomly, but an equal number of subjects receive each treatment in each phase, as depicted in Table 1. Thus, in case of two treatments A and B, one group gets the treatment in the order AB, and the second group in the reverse order. This is done to avoid the occurrence of possible sequence or period effects.[8] A similar allocation is done in case of a three-treatment crossover design (three-period, three-treatment crossover design).

For several drugs a great inter-subject variability in clearance is observed. The intra-subject coefficient of variation (approximately 15%) is usually substantially smaller than that between subjects (approximately 30%), and therefore, crossover designs are generally recommended for bioequivalence studies.[9, 10]

The primary advantage of the crossover design is that since the treatments are compared on the same subject, the inter-subject variability does not contribute to the error variability. If the drug under investigation and its metabolites have an extremely long half life, a parallel group design may be indicated. In a parallel group design, subjects are divided randomly into groups, each group receiving one treatment only. Thus, each subject receives only one treatment In a parallel design, although one does not have to worry about sequence, period or carry over effects, or dropouts during the study, the inter-subject variability being very high, the sensitivity of the test is considerably reduced, thus requiring a larger number of subjects compared to a crossover design, to attain the same sensitivity. Inherent in both the crossover and parallel designs are the three fundamental statistical concepts of study design, namely randomization, replication and error control.[11, 12] Randomization implies allocation of treatments to the subjects without selection bias. Consequently, randomization is essential to determine an unbiased estimate of the treatment effects. Replication implies that a treatment is applied to more than one experimental unit (subject) to obtain more reliable estimates than is possible from a single observation and hence provides a more precise measurement of treatment effects. The number of replicates (sample size) required will depend upon the degree of differences to be detected and inherent variability of the data, replication is used concomitantly 7 variability.

The various pharmacokinetic parameters (AUC, Cmax) derived from the plasma concentration-time curve are subjected to ANOVA in which the variance is partitioned into components due to subjects, periods and treatments. The classical null hypothesis test is the hypothesis of equal means, H0: $\mu T = \mu R$ (i.e. products are bioequivalent), where μT and μR represent the expected mean bioavailabilities of the test and reference drug, respectively.

The alternate hypothesis therefore is H1: $\mu T \neq \mu R$ (i.e. products are bioinequivalent). There are two ways of designing the experiment: (i) Design 1 (parallel group design): divide the subjects into two groups and assign one treatment to each group and; (ii) Design 2 (crossover design): consider each subject as a block and then apply both the treatments to each block (subject) on two different occasions. In a parallel group design, only the variability due to the treatment is separated out, whereas in the crossover design, variability due to treatment, block (subject) and period are separated out from error variability. Consequently, the error sum of squares (SSE) is greater in the parallel design for a specific sample size (Error sum of squares in Design 1 (SSE1) = Error sum of squares in Design 2 (SSE2) + (subjects sum of squares) SSS2 + (periods sum of squares) PSS2. As degrees of freedom for SSE are the same in both the designs (for two-treatment case), the error mean sum of square for Design 1 (MSE1) will be greater than the error mean sum of square for Design 2 (MSE2),[12] i.e. error variability is greater in the parallel group design compared to the crossover design.

Table 1: Analysis of variance (ANOVA) table for t-period, t-treatment crossover design

Sources of variance	Degree of freedom (DF)	Sum of squares (SS)	Mean of squares (MS)	F statistic
Treatment	T-1	SST	MST	MST/MSE
Subjects	N-1	SSS	MSS	MSS/MSE
Period	t-1	SSP	MSP	MSP/MSE
Error	(t-1)(n-2)	SSE	MSE	
Total	tn-1			

T is no. of treatments, N is no. of subjects, SST-Sum of squares due to treatments, SSS-Sum of squares due to subjects, SSP-Sum of squares due to period, SSE-Sum of square due to error, MST-Mean sum of squares due to treatments, MSS-Mean sum of squares due to subjects, MSP-Mean sum of squares due to period, MSE-Mean sum of squares due to error.

Table 2: Design 1 A comparison of ANOVA for parallel group design and 2-treatment, 2-period crossover design with n subjects

Sources of variations	Sum of squares (SS)	Degree of freedom (DF)	Mean sum of squares (MSS)	F Statistic
Between treatments	SST1	1	MST1	MST1/MSE1
Error	SSE1	N-2	MSE1	
Total		n-1		

Design 2

In ANOVA, the mean sum of squares due to a factor is compared with the mean sum of squares due to error (e.g. F= MST / MSE), and if these are comparable, no difference between the levels of a factor is concluded, otherwise a difference is concluded. Suppose there is a difference in treatments i.e. the treatment mean sum of squares is larger than the error mean sum of squares. Then the chances of the treatment mean sum of squares being larger than the error mean sum of squares are more in Design 2 compared to Design 1, since MSE2 < MSE1. Therefore, chances of showing a statistically significant difference (when actually there is a difference) are higher in Design 2 compared to Design 1. This is equivalent to saying that Design 2 is more powerful than Design 1. This reveals how the power of a test is influenced by the design of the experiment. In ANOVA, the ratio of the formulations' mean sum of squares to the error mean sum of squares gives an F-statistic to test the null hypothesis H0 $\mu T=\mu R$. This provides a test of whether the mean amount of drug absorbed from the test formulation is identical to the mean amount of drug absorbed from the reference. The test of this simple null hypothesis of identity is of little interest in bioequivalence studies, since the answer is always negative. This is because we cannot expect the mean amounts of drug absorbed from two different formulations or two different batches of the same formulation to be identical. They may be very nearly equal, but not identical. Also, if the trial is run under tightly controlled conditions (resulting in a small error mean sum of squares in the analysis) and if the number of subjects is large enough, no matter how small the difference between the formulations, it will be detected as significant. Thus the detection of the difference (which as indicated above, will always exist) becomes simply a function of sample size, and since the probable magnitude of the difference is the critical factor, this gives rise to two anomalies:

- A large difference between two formulations which is nevertheless not statistically
- Significant if error variability is high and/or sample size not large enough.
- A small difference, probably of no therapeutic importance whatsoever, that is shown to be statistically significant if error variability is minimal and/or sample size adequately large.

The first case suggests a lack of sensitivity in the analysis, and the second an excess of it. Consequently, any practice that increases the variability of the study (sloppy designs, assay variability and within formulation variability) would reduce the chances of finding a significant difference and hence improve the chances of concluding bioequivalence.

The FDA[13] therefore, recognized that a finding of no statistical significance in the first case was not necessarily evidence of bioequivalence and consequently asked for a retrospective examination of the power of the test of null hypothesis. Specifically, it was mandated that the test of equivalence have at least an 80% power of detecting a 20% difference between μT and μR (the 80/20 rule), where 20% was apparently arbitrarily chosen to represent the minimum difference that could be regarded as of therapeutic importance. However, there was no such criterion for the second case, and consequently if a very small difference was shown to be statistically significant, the conclusion that the difference was negligible and that the formulations could be considered bioequivalent was based solely on clinical judgment. It was therefore realized that the testing of the simple null hypothesis was inadequate and inappropriate and what was needed was not a test of whether the two formulations were identical but some degree of assurance that the mean amount of drug absorbed using the test formulation was close to the mean amount absorbed in case of the reference. The test hypothesis therefore, needed to be reformulated.

Table 3: Design 2A comparison of ANOVA for parallel group design and 2-treatment, 2-period crossover design with n subjects

Sources of variation	Sum of squares (SS)	Degree of freedom (DF)	Mean sum of squares (MSS)	F statistic
Between treatments	SST2	1	MST2	MST2/MSE2
Between blocks (subjects)	SSS2	N-1	MSS2	
Between periods	SSP2	1	MSP2	
Errors	SSE2	N-2	MSE2	
Total		2n-1		

Another argument which favoured an alternate approach to ANOVA for bioequivalence determination was the magnitude of the manufacturer's risk versus the consumer's risk. Manufacturer's risk is defined as the probability of rejecting a formulation which is in fact bioequivalent. In other words, the manufacturer's risk is the probability (α) of rejecting H0

When H0 is true (Type I error), and this risk was fixed at α =0.05 by the FDA (1977).[11] similarly, the consumer's risk is defined as the probability (β) of accepting a formulation which is bioinequivalent, i.e. accepting H0 when H0 is false (Type II error).

By introducing the requirement that the power (1- β) of the test should be 80%, the FDA sought to restrict the consumer's risk "β" to 20%. This, however, was not a satisfactory solution for either the consumer or the regulatory agencies. In a regulatory environment, it makes sense that the regulatory authorities control the consumer's risk and let the pharmaceutical company decide how much manufacturer's risk they are willing to accept. As indicated, neither of these risks are formally identified or controlled when using the ANOVA F-test for treatments, even with the 80/20 rule. Also the FDA guidelines[7] for bioavailability studies state that "Products whose rate and extent of absorption differ by 20% or less are generally bioequivalent". This implies that in the case of bioequivalence studies the interest is not in testing the null hypothesis of equality but in assessing the difference in two treatments. Bioequivalence is concluded if this difference is within 20% of the reference mean.[13]

Importance Of Bioavailability/ Bioequivalence Studies

A universal approach about comparative bioavailability

Most bioavailability studies, whether for a new or generic product, possess a common theme. A test is conducted to identify the quantitative nature of a specific product comparison. This comparison for a new drug may be, for example, to assess the performance of an oral formulation relative to that of an intravenous dose, or perhaps the performance of a modified-release formulation in comparison to a conventional capsule. For a generic product, it is typically a comparison of a competitive formulation with a reference drug. Such commonality surrounding comparative bioavailability studies suggests a universal experimental approach.

Comparative bioavailability studies about new drugs (NDA)

The initial oral formulation for a new drug is frequently used to conduct early human studies of safety and efficacy. Often, early oral bioavailability information about the drug (and this initial formulation) is obtained by means of studies comparing it with an intravenous dose and a solution of the drug they employ the Universal Approach wherein the comparator is an intravenous dose or perhaps a solution of the drug.

Comparative bioavailability about generic drugs (ANDA)

When a manufacturer thereby wishes to gain therapeutic equivalence by introducing a competitive generic product into the market place, it is not necessary to conduct the full array of trials needed for the first product. If equivalence has been demonstrated, according to prescribed study requirements appropriately determined metrics the generic product by inference is regarded as therapeutically equivalent to the innovative drug product.

Testing under fasting conditions/Testing under fed conditions

When the particular drug is not showing any expected results, then the drug is tested under fasting conditions using bioequivalence studies.

The drug can also be tested under fed conditions to meet all conditions as per regulatory norms.[14, 21]

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