Gouthami A. *et al.* / *International Journal of Phytopharmacology*, 4(2), 2013, 74-84.

e- ISSN 0975 – 9328
Print ISSN 2229 – 7472

International Journal of Phytopharmacology

Journal homepage: www.onlineijp.com

IJP

A REVIEW ON GENERAL CONCEPTS OF DESIGN AND CONDUCT OF BIOEQUIVALENCE STUDIES

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ABSTRACT

Bioavailability (BA) and bioequivalence (BE) studies play a major role in the drug development phase for both new drug products and their generic equivalents, and thus attract considerable attention globally. Bioequivalence (BE) means the absence of a greater-than-allowable difference between the systemic bioavailability of a test product and that of a reference product. The value of testing two one-sided null hypotheses of non-equivalence at a significance level of 0.05, and the importance of estimating a 90% confidence interval of the ratio (test/reference) of mean AUC and C_{max} values, and of the difference between mean t_{max} values, are now recognized and form the current standards for BE. The Study design should be based on a reasonable knowledge of the pharmacodynamics and/or the pharmacokinetics of the active substance in question. The design and conduct of the study should follow ICH/ EU regulations on Good Clinical Practice, including reference to an Ethics Committee. This article briefly reviews the BA/BE concepts, various basic regulatory considerations, design and conduct of BA/BE studies.

Key words: Bioavailability, Bioequivalence, Generic drugs, Pharmacokinetics.

INTRODUCTION

Life expectancy of patients has increased globally during the last three decades due to the new drug discovery (brand-name drugs) as well as generic drug production. The rising cost of medication has been contributing to the total overall cost of health care and thus receives considerable attention globally. A major strategy for lowering the cost of medication, and thereby reducing its contribution to total health care costs, has been the introduction of generic equivalents of brand-name drugs (Midhal *et al*., 2009). This strategy has been effective in reducing total prescription cost by 11% without sacrificing quality (Haas *et al*., 2005). Generic drugs have captured more than 65% of the global market and account for 66% of prescriptions filled in the United States but for less than 13% of the cost (Shrank *et al*., 2009).

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Thus, because of the importance of generic drugs in health care, it is imperative that the pharmaceutical quality, safety, and efficacy of generics should be reliably compared with the corresponding innovator drugs (brand-name drugs).Consequently, on the basis of simple pharmacokinetic concepts and parameters, bioavailability and bioequivalence studies have been established as acceptable surrogates for expensive, complicated and lengthy clinical trials, and are used extensively worldwide to establish and ensure consistent quality and a reliable, therapeutically effective performance of marketed dosage forms.

Bioavailability reflects the extent of the systemic availability of the active therapeutic moiety and is generally assessed by measuring the 'area under the concentration time curve' (AUC), the peak plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}). For a drug that obeys linear pharmacokinetics, the AUC and C_{max} values increase proportionately with the dose (Gibaldi *et al*., 1982). Consequently, if two formulations/ dosage forms of the same drug exhibit comparative AUC values, they are considered to have similar systemic

availability. The bioavailability of an oral dosage form or a drug is generally compared with an intravenous solution (100% standard), to determine the absolute bioavailability. In case of drugs which obey non-linear kinetics, the changes in AUC and C_{max} values are not proportional to the dose administered (Gibaldi *et al*., 1982). This is because either one or more of the processes which handle the drug i.e. absorption, distribution, metabolism and excretion are saturated i.e. their capacity has been exceeded within the therapeutic concentration range of the drug (substrate). In this situation, the plasma concentration-time profile cannot be used as an indicator of absolute bioavailability. The latter has to be then assessed by measuring the extent of the drug and its metabolites excreted in the urine.

The comparative bioavailability assessment of two or more formulations of the same active ingredient to be administered by the same route is termed bioequivalence. Bioequivalence studies compare both the rate and extent of absorption of various multisource drug formulations with the innovator (reference) product, on the basis that if two formulations exhibit similar drug concentration-time profiles in the blood/plasma, they should exhibit similar therapeutic effects. For an unapproved generic dosage form to be marketed and accepted as therapeutically equieffective to the innovator product, it must establish bioequivalence with the innovator product, in vivo. Bioequivalence studies provide a quality control tool to monitor production and manufacturing changes (Grizzle, 1965).

Definitions: (USFDA guidelines), (Guidance for industry,CDER,2003),(EMEA,2010)

Brand-name drug: A brand-name drug is a drug marketed under a proprietary, trademark-protected name.

Generic drug: A generic drug is the same as a brandname drug in dosage, safety, strength, how it is taken, quality, performance, and intended use.

Pharmaceutical equivalents: Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredient(s), have the same dosage form and route of administration, and are identical in strength or concentration.

Pharmaceutical alternatives: These are the drug products that contain the same active moiety but contain different chemical forms such as esters or salts of the active moiety or they may differ from the innovator's product in the dosage form or strength.

Reference listed drug (RLD): A reference listed drug is an approved drug product to which new generic versions are compared to show that they are bioequivalent.

Bioavailability (BA): The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

Bioequivalence (BE): The absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Guidelines to be considered for these studies:

Bioavailability and Bioequivalence studies are required by regulations to ensure therapeutic equivalence between a pharmaceutically equivalent test product and a reference product. Several in vivo and in vitro methods are used to measure product quality.

When bioequivalence studies are necessary and types of studies 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:

a. Oral immediate release drug formulations with systemic action when one or more of the following criteria apply:

i) Indicated for serious conditions requiring assured therapeutic response;

ii) Narrow therapeutic window/safety margin; steep dose-response curve;

iii) Pharmacokinetics complicated by variable or incomplete absorption or absorption window, nonlinear pharmacokinetics, pre-systemic elimination/high first-pass metabolism >70%;

iv) Unfavorable physicochemical properties, e.g., low solubility, instability, meta-stable modifications, poor permeability, etc.;

v) Documented evidence for bioavailability problems related to the drug or drugs of similar chemical structure or formulations;

vi) Where a high ratio of excipients to active ingredients exists.

b. Non-oral and non-parenteral drug formulations designed to act by systemic absorption (such as transdermal patches, suppositories, etc).

c. Sustained or otherwise modified release drug formulations designed to act by systemic absorption.

d. Fixed-dose combination products with systemic action.

e. Non-solution pharmaceutical products which are for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal, etc. application) and are intended to act without systemic absorption. In these cases, the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required 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:

i) Early and late clinical trial formulations

ii) Formulations used in clinical trials and stability studies, if different

iii) Clinical trial formulations and to be marketed drug products

iv) Other comparisons, as appropriate in each comparison, the new formulation or new method of manufacture shall be the test product and the prior formulation (or respective method of manufacture) shall be the reference product.

When bioequivalence studies are not necessary:

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

a. When new drugs are to be administered parenterally (e.g., intravenous, intramuscular, subcutaneous, intrathecal administration etc.) as aqueous solutions and contain the same active substance(s) in the same concentration and the same excipients in comparable concentrations;

b. When the new drug is a solution for oral use, and contains the active substance in the same concentration, and does not contain an excipient that is known or suspected to affect gastro-intestinal transit or absorption of the active substance;

c. When the new drug is a gas;

d. When the new drug is a powder for reconstitution as a solution and the solution meets either criterion (a) or criterion (b) above;

e. When the new drug is an otic or ophthalmic or topical product prepared as aqueous solution and contains the same active substance(s) in the same concentration(s) and essentially the same excipients in comparable concentrations;

f. When the new drug is an inhalation product or a nasal spray, tested to be administered with or without essentially the same device as the reference product, prepared as aqueous solutions, and contain the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations. Special in vitro testing is required to document device performance comparison between reference inhalation product and the new drug product.

For (e) and (f) above, the applicant is expected to demonstrate that the excipients in the new drug are essentially the same and in comparable concentrations as those in the reference product. In the event this information about the reference product cannot be provided by the applicant, in vivo studies need to be performed.

The pertinent situations in which bioequivalence studies are required include:

a. When the proposed marketed dosage form is different from that used in pivotal clinical trials,

b. When significant changes are made in the manufacture of the marketed formulation.

c. When a new generic product is tested against the innovator's marketed product.

Design and conduct of studies:

Pharmacokinetic Studies:

Study Design: The basic design of an in-vivo bioavailability study is determined by the following and brief process of study design was given in fig.1.

i) What is the scientific question(s) to be answered?

ii) The nature of the reference material and the dosage form to be tested.

iii) The availability of analytical methods.

iv) Benefit-risk ratio considerations in regard to testing in humans.

The study should be designed in such a manner that the formulation effect can be distinguished from other effects.

Concepts of crossover design:

As recommended by the US FDA (1992) (FDA guidance, 2001), in most bioequivalence trials, a "test" formulation is compared with the standard/innovator "reference" formulation, 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. 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 (Grizzle, 1965). A similar allocation is done in case of a three-treatment crossover design (three-period, three-treatment crossover design).

For several drugs 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 (Zar JH, 1984; Armitage, 1973). 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/or 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 (Cochran *et al*., 1957; Fisher, 1966). 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.

Single-dose studies generally suffice. However situations as described below may demand a steady-state study design: i) Dose or time-dependant pharmacokinetics. ii) Some modified release products (in addition to single dose investigations) iii) Where problems of sensitivity preclude sufficiently precise plasma concentration measurements after single-dose administration. IvIf 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.

Study Population:

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:

i) The error variance associated with the primary characteristic to be studied as estimated from a pilot experiment, from previous studies or from published data.

ii) The significance level desired: usually 0.05

iii) The expected deviation from the reference product compatible with bioequivalence.

iv)The required (discriminatory) power, normally 80% to detect the maximum allowable difference (usually 20%) in primary characteristics to be studied.

The number of subjects recruited should be sufficient to allow for possible withdrawals or removals (dropouts) from the study. It is acceptable to replace a subject withdrawn/drop out from the study once it has begun provided the substitute follows the same protocol originally intended for the withdrawn subject and he/she is tested under similar environmental and other controlled conditions. However, the minimum number of subjects should not be less than 16 unless justified for ethical reasons. Sequential or add-on studies are acceptable in specific cases e.g. where a large number of subjects are required or where the results of the study do not convey adequate statistical significance. In all cases the final statistical analysis must include data of all subjects or reasons for not including partial data as well as the un-included data must be documented in the final report.

Selection Criteria for Subjects:

To minimize intra and inter individual variation subjects should be standardized as much as possible and acceptable. 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. Risks to women of childbearing potential should be considered on an individual basis. Women should be required to give assurance that they are neither pregnant, nor likely to become pregnant until after the study. This should be confirmed by a pregnancy test immediately prior to the first and last dose of the study. Women taking contraceptive drugs should normally not be included in the studies. If the drug product is to be used predominantly in the elderly attempt should be made to include as many subjects of 60 years of age or older as possible. If the drug product is intended for use in both sexes attempt should be made to include similar proportions of males and females in the studies.

For a drug representing a potential hazard in one group of users, the choice of subjects may be narrowed, e.g., studies on teratogenic drugs should be conducted only on males. For drugs primarily intended for use in only males or only females – volunteers of only respective gender should be included in the studies. For drugs where the risk of toxicity or side effects is significant, studies may have to be carried out in patients with the concerned disease, but whose disease state is stable. They should be screened for suitability by means of a comprehensive medical examination including clinical laboratory tests, an extensive review of medical

history including medication history, use of oral contraceptives, alcohol intake, and smoking, use of drugs of abuse. Depending on the study drugs therapeutic class and safety profile, special medical investigations may need to be carried out before, during and after the study.

Study Conditions:

Standardization 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 been minimised. 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 Points/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 (normally 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 t_{max}, 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 data/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 C_{max} and t_{max} 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:

i) Where the drug has a long terminal elimination half-life and blood concentrations after a single dose cannot be followed for a sufficient time.

ii) Where assay sensitivity is inadequate to follow the terminal elimination phase for an adequate period of time.

iii) 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. many cytotoxics

iv) For modified-release products where it is necessary to assess the fluctuation in plasma concentration over a dosage interval at steady state.

v) For those drugs which induce their own metabolism or show large intra- individual variability.

vi) For enteric-coated preparations where the coating is innovative.

vii) For combination products where the ratio of plasma concentration of the individual drugs is important.

viii) For drugs that exhibit non-linear (i.e., dose- or time-dependent) pharmacokinetics.

ix) Where the drug is likely to accumulate in the body. In steady state studies, the dosing schedule should follow the clinically recommended dosage regimen.

Characteristics to be investigated during bioavailability / bioequivalence studies: In most cases evaluations of bioavailability and bioequivalence will be based upon the measured concentrations of the active drug substance(s) in the biological matrix. In some situations, however, the measurements of an active or inactive metabolite may be necessary. These situations include (a) where the concentrations of the drug(s) may be too low to accurately measure in the biological matrix, (b) limitations of the analytical method, (c) unstable drug(s), (d) drug(s) with a very short half-life or (e) in the case of prodrugs.

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: (a) the enantiomers exhibit different pharmacodynamic characteristics (b) the

enantiomers exhibit different pharmacokinetic characteristics (c) primary efficacy / safety activity resides with the minor enantiomer (d) 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.

The following pharmacokinetic parameters are required for submission:

- Plasma concentrations and time points
- Subject, period, sequence, treatment
- AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, λ_z and $t_{½}$.
- Intersubject, intrasubject, and/or total variability, if available
- C_{min} (concentration at the end of a dosing interval),
- C_{av} (average concentration during a dosing interval),

Degree of fluctuation [$(C_{max}-C_{min})/C_{av}$], and Swing [$(C_{max}-C_{min})/C_{min}$] if steady-state studies are employed (Indian regulatory guidelines), (Guidance for industry, CDER 2002).

e) The following statistical information required for AUC_{0-t}, $AUC_{0-\infty}$ and Cmax:

- Geometric mean
- Arithmetic mean
- Ratio of means
- Confidence intervals

Logarithmic transformation should be provided for measures used for BE demonstration.

Bioanalysis: Bioanalysis is a term generally used to describe the quantitative measurement of a compound (drug) or its metabolite in biological fluids, primarily blood, plasma, serum, urine, or tissue extracts (James *et al*., 2004). It typically consists of two important components

1) Sample preparation and

2) Detection of the desired compound using a validated method.

For the most part, traditional BE studies have been carried out on the basis of measurement of only the parent drug in body fluids such as plasma or serum. In some cases, however, monitoring a metabolite, or the parent and metabolite(s), may be more appropriate. A number of reasons for use of metabolite data have been put forward (Midha *et al*., 2004) such as,

1) The parent is an inactive prodrug,

2) The parent drug is metabolized rapidly to an active metabolite, and

3) The parent drug and a metabolite both have therapeutic activities but the metabolite is present in higher concentrations when the parent drug is rapidly and extensively metabolized such that only metabolite(s) data are available (Chen *et al*., 2001).

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) concentration in a specific biological matrix. The characteristics of a bioanalytical method essential to ensure the acceptability of the performance and the reliability of analytical results are: (1) stability of the stock solutions and of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage; (2) specificity; (3) accuracy; (4) precision (5) limit of quantification and (6) response function.

The validation of a bioanalytical method should comprise two distinct phases: (1) the pre study phase in which the compliance of the assay with the six characteristics listed above is verified and (2) the study phase itself in which the validated bioanalytical method is applied to the actual analysis of samples from the biostudy mainly in order to confirm the stability, accuracy and precision.

BE metrics and data treatment: (Midhal *et al*., 2009), (Chen *et al*., 2001), (Henney, 1999).

The most frequent data treatment involves analysis of variance using a suitable program such as SAS® (Statistical Analysis System, SAS Institute, Cary, NC) or WinNonlin® (Pharsight Corporation, St. Louis, MO) so that contributions from subject, period, product/formulation, and interactions between these can be examined. Geometric mean ratios and log transformed data are examined to test the hypothesis that the 90% confidence interval of extent (AUC_{0-t} and $AUC_{0-\infty}$) and the maximum concentration (C_{max}) fall within the acceptance limits of 80% to 125%. More recently, other data treatments have been popular, which include partial area measurements and exposure metrics including C_{max} /AUC, especially with highly variable drugs (HVDs), and with drugs having a long terminal $t_{½}$, specialized dosage forms, and/or whose time to C_{max} is considered important (eg, certain analgesics). In all of these cases, the objective has been to err on the side of protecting the consumer while at times increasing risk to the manufacturer. Hence, over the last 15 years, considerable debate has occurred globally about the fundamental scientific rationale used to establish BE for some of these "special" cases, in an effort to solve these issues associated with harmonization of drug equivalence approaches.

Statistical interpretation of bioequivalence data:

After the data has been collected, statistical methods must be applied to determine the level of significance of any observed difference in the rate and or extent of absorption in order to establish bioequivalence between two or more drug products. The general statistical deliverables for a single-dose crossover BE study include summary statistics, ANOVA, 90%

confidence interval, ratio analysis, and intra-subject variability in addition to sequence, treatment, and period effects. The commonly adopted approaches to determine statistical differences are

Analysis of variance:

The various pharmacokinetic parameters 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: μT = μR (i.e., products are bioequivalent), where μT and μR represent the expected mean bioavailabilities of the test and reference products, respectively. The alternate hypothesis therefore is H1: μT ≠ μR (i.e., products are bioinequivalent) (Henney, 1999), (Pargal *et al*., 2004).

Confidence interval approach:

Westlake (Westlake,1972) was the first to suggest the use of confidence intervals as a BE test to evaluate whether the mean amount of drug absorbed using the test formulation was close to the mean amount absorbed of the reference product. This is based primarily on average BE (ABE), wherein the average values for the pharmacokinetic parameters were determined for the test and reference products and compared using a 90% confidence interval for the ratio of the averages using a two one-sided *t*-tests procedure (Schuirmann, 1987). A 90% confidence interval about the ratio of means of the two drug products must be with in ±20% for bioavailability parameters such as AUC or C_{max} i.e. the difference between the bioavailabilities of the test product should not be greater than± 20% of the average of reference product (between 80 and 120%) (Westlake, 1972). When log transformed data are used; the 90% confidence interval is set at 80-125%.These confidence limits are also termed as bioequivalence interval.

Regulatory norms considering in study:

Australia

In Australia, the Therapeutics Goods Administration (TGA) considers preparations to be bioequivalent if the 90% confidence intervals (90% CI) of the transformed natural log ratios, between the two preparations, of Cmax and AUC lie in the range 0.80-1.25. Tmax should also be similar between the products (Birkett2003). There are tighter requirements for drugs with a narrow therapeutic index and/or saturable metabolism thus no generic products exist on the Australian market for digoxin or phenytoin for instance.

Europe

According to European regulations EMEA-CPMP, Note for Guidance on the investigation of Bioavailability and Bioequivalence, London, July 2001 CPMP/EWP/QWP/1401/98 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 transformed natural log ratios, between the two preparations, of C_{max} and AUC lie in the range 0.80-1.25.

United States

The United States Food and Drug Administration (FDA) has defined bioequivalence as, "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."

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 "food-effect" study. A food-effect study requires the same statistical evaluation as the fasting study, described above.

Applications of BA/BE studies:

Comparative bioavailability: a universal approach

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 product. Such commonality surrounding comparative bioavailability studies suggests a universal experimental approach.

Comparative bioavailability studies for 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/or 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 for generic drug products (ANDA)

When a manufacturer thereby wishes to gain therapeutic equivalence by introducing a competitive generic product into the marketplace, it is not necessary to conduct the full array of trials needed for the first (innovative) 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: When the particular drug is not showing any expected results, then the drug is tested under fasting conditions using BE trials.

Testing under fed conditions: The drug can also be tested under fed conditions to me*et al*l conditions as per regulatory norms (Blanchard *et al*., 1979; Abdou, 1989; Chow *et al*., 1992).

Figure1. Brief process of bioequivalence study design and protocol approval Concepts of crossover design:

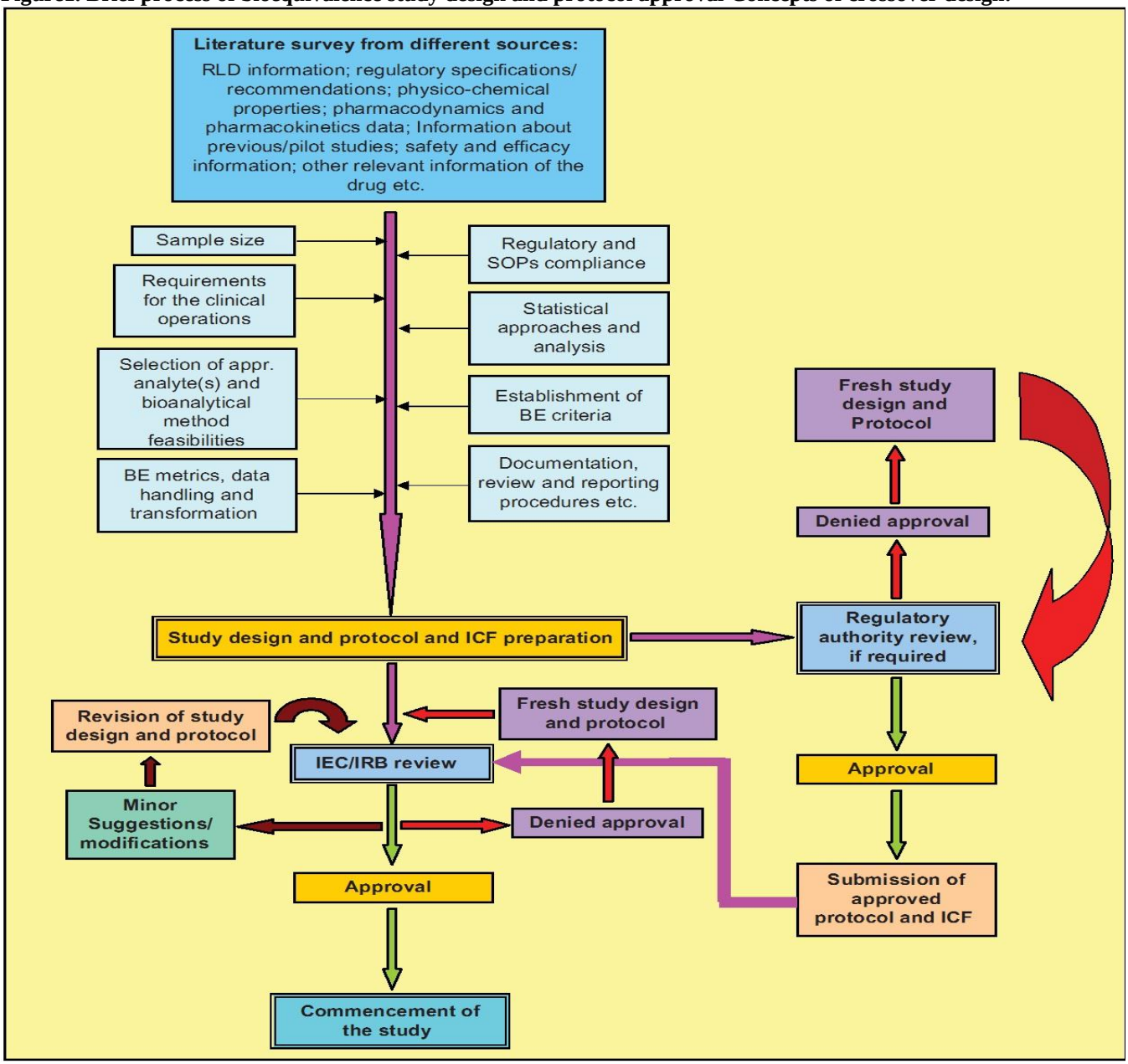


Figure 2. Brief representation of work flow of bioavailability/bioequivalence study

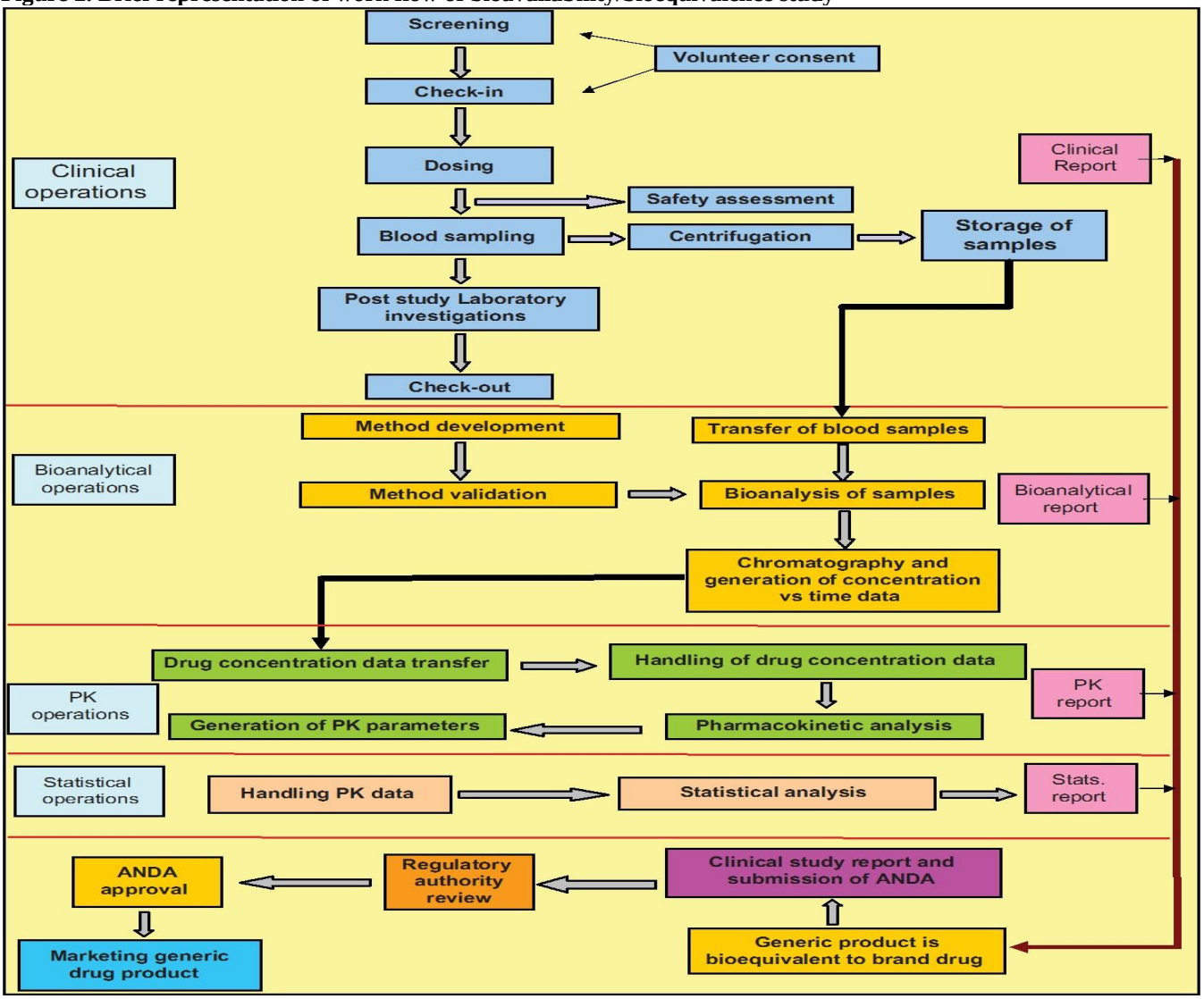
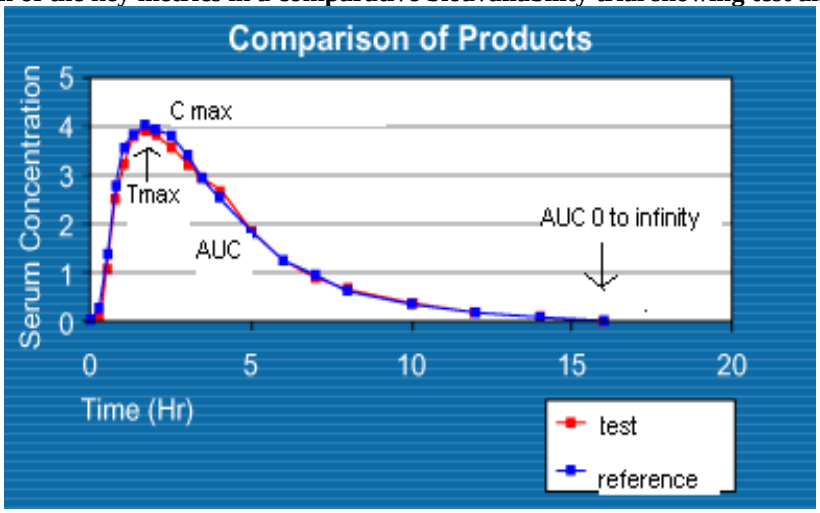


Figure 3. An illustration of the key metrics in a comparative bioavailability trial showing test and reference products



CONCLUSION

The review was concluded that bioavailability and bioequivalence studies have been established as acceptable surrogates for expensive, complicated and lengthy clinical trials, and are used extensively worldwide to establish and ensure consistent quality and a reliable, therapeutically effective performance of marketed dosage forms. This continuing success story of BA/BE is based on the contribution to efficacy, safety, and quality by international regulatory authorities, pharma industry researchers, academic researchers, and indeed the efforts from ICH, WHO, and various international conferences. However, a lot remains to be done, especially to promote global harmonization of BA/BE approaches, which should focus on uniformity, standardization of nomenclature, agreement on general concepts, consideration of BE criteria and objectives, all of which reflect regulatory decision-making standards, as well as ensuring product quality over time for both innovator and generic drugs. To achieve these objectives efforts should continue from international health organizations, pharmaceutical industries, researchers, and regulatory authorities to understand and to develop more efficient and scientifically valid approaches to assess BE, and develop generic drugs in a cost-effective manner.

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