# BIOEQUIVALENCE STUDIES – A REGULATORY PERSPECTIVE

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## Summary

The concept of bioequivalence is well established in the regulated drug markets. Due to the high number of studies, significant number bioequivalence related problems are also observed. A number of studies of marketed drug products which includes the same therapeutic ingredient from different manufacturers have revealed significant differences in rate and extent of drug absorption. There are regulatory bodies from different countries which provide standard requirements for conducting and reporting these bioequivalence studies. The recommendations of few such regulations for bioequivalence studies are enumerated in this review. As more number of generic drug makers are pushing for faster approvals, regulatory bodies should be more vigilant in maintaining the right standards for designing and reporting of these bioequivalence studies.

**Keywords:** Bioequivalence studies, bioavailability, regulatory guidelines, pharmacokinetics

## Introduction

To demonstrate therapeutic equivalence between two drug products bioequivalence (BE) studies are considered to be one of the widely and commonly used methods[1-3]. While using these studies, the pharmaceutical companies can save lot of time and cost for the development of their molecules. This is the reason why the bioequivalence have received major importance from the pharmaceutical companies, contract manufacturing organizations and some institutions. While planning, designing, conducting, analyzing and reporting of these studies requires lot of regulatory attention. These bioequivalence studies focus on release characteristics of the formulation and subsequent absorption into the systemic circulation and acts as an important element for submission of new or abbreviated drugs or its supplements to the respective

regulatory authority approvals[1]. As there are many numbers of generic products are available in the international markets, it has become a public concern that these products are similar to that of innovator in terms of safety and efficacy. Therefore a valid statistical evaluation is necessary to guarantee the safety and efficacy of these products[2].

These regulatory guidelines are intended to provide recommendations to pharmaceutical industries or applicable stakeholders about the planning of these studies. There are various regulatory recommendations to carry out these bioequivalence studies and depends on country for which the submission is planned[3-14, 52-56]. WHO has developed a standard bioequivalence trial information form (BTIF) and the generic drug products of HIV/AIDS, tuberculosis & malaria are to be submitted as per this form along with required documents[15]. The regulatory requirements for orally administered drug products are well established but for other classes of products, including biological (biosimilars) and product manufactured by biotechnology, the concept of bioequivalence remains complex and not established[16-19]. Only EMEA has a guideline on developing similar biological medicinal products and other countries would follow soon as several of these molecules are going off patent in near future[20, 21].

This review makes an attempt to establish the differences between the various regulatory guidelines for bioequivalence studies. The differences are enumerated based on the study design, type of drug product, subject selection, drug dosing, bioanalytical methodology, moieties to be measured, sampling schedules and pharmacokinetic parameters.

## Study design

The study design should be such that the formulation effects should be distinguished from other effects[3]. To measure the pharmacokinetic properties of the active ingredient of the drug a suitable biological matrix such as blood, plasma and/or serum should be collected for analysis. If the validated analytical method is not available then the sponsor can opt for conducting a pilot study with small number of subjects. If the sample size is found to be very high based on the calculations and assumptions a pilot study can be planned and results can be simulated for the pivotal bioequivalence study. Most of the regulatory authorities recommend for comparative, nonreplicate, two periods, two-sequence crossover study designs for the oral drug products, which includes immediate and modified release formulations[1-14]. The choice of selecting parallel (for long half-life drugs), replicate (for highly variable drugs) or nonreplicate design depends on the statistical recommendations and type of information to be gathered from these studies.

The studies will be carried out using adequate number of healthy subjects in a statistically powered design. The choice of sample size and the level of statistical significance should be justified in the protocol. As per Anderson, Liu and Chow, drug switchability would be assured by assessing bioequivalence within individual subjects[2]. The subjects should be administered either test or reference product with specified amount of water under fasting conditions. If the pharmacokinetics of the drug is affected by presence of food then well designed food-effect bioequivalence study should be conducted[7, 9]. The recommendations for food-effect studies may vary from country to country based on the social and cultural variations but the appropriate

justification should be provided for the type of food given. These studies are majorly applied for modified release dosage forms.

As per EMEA, if the Summary of Product Characteristics (SPC) defines food intake based on the pharmacokinetic properties i.e, increase in bioavailability, to decrease adverse events and/or improve tolerability fed studies should be planned in addition to the fasting studies. Fluid and food intake, physical activity, and consumption of certain dietary products must be carefully restricted during the study course so that these factors will not influence drug absorption or elimination[22].

**Type of drug product**

Most of the regulatory agencies recommend single dose studies with orally administered drugs which includes immediate and modified release dosage forms. The sensitivity in assessing the drug release pattern from these dosage forms is very evident with single dose studies. There are instances where the regulation asks for conducting the multiple dose studies. These can be enumerated as, if the

- drug is embedded in modified release dosage form
- drug is following non-linear pharmacokinetics
- sensitivity of the analytical method is poor after single dose administration
- drug demonstrates high intra-subject variability

While designing these multiple dose studies, importance should be given on selection of appropriate dose and sampling points to demonstrate steady state[1-14].

BE studies are waived for solutions on the assumption that release of the drug substance from the drug product is self-evident and that the solutions do not contain any excipients that significantly affects drug absorption[11]. If the application is for the generic drug then the test product should be compared with the corresponding dosage form of the reference product. The choice of selecting the strength, dosage and formulation of the reference product should be justified in the protocol[3]. The test product should be manufactured under GMP conditions, the batch records and comparative in-vitro dissolution profiles should be maintained. While selecting a highly variable drug (HVD), due to its poor formulation characteristics the test drug may not show bioequivalent to that of reference drug[8, 23].

**Subject selection**

The subject selection is purely based on the power function of the parametric statistical test procedure applied. A major objective of subject selection criteria is a reduction in pharmacokinetic variability attributed to subject's characteristics. A written informed consent should be obtained from all the subjects participating in the BE studies. Sponsor should also take care of adequate sample size to accommodate the dropouts because replacing the subjects may complicate the statistical analysis[1]. Agencies like CDSCO, India recommends to replace a subject withdrawn/drop out from the study once it has begun provided the substitute must follow the same protocol and controlled conditions. If for any reason other than adverse event (AE) or

serious adverse event (SAE) the subject withdraws the results of all samples that were measured must be included in the report[10]. If subjects drop out of the study for personal reasons, the subject's blood samples do not have to be assayed[5]. Japan's National Institute of Health allows the addition of subjects to increase the power of a failed BE study. However, the add-on subjects cannot be less than half the number in the original study[13, 24].

Most of the regulatory agencies recommend minimum number of subjects to be enrolled but the decision lies with the sponsor. The general recommendation is to enroll normal healthy subjects of either sex, preferably non-smokers and non-alcoholics. The sponsor should also consider the appropriate demographic profile to minimize the inter-subject variability. If there are safety concerns as in the case of cytotoxic or antiretroviral or specific population (patients) and gender (females in case of oral contraceptives) should be selected[25, 26]. Other factors such as age, body size, nutritional status, tobacco use, disease states, concurrent drug use, and substance abuse must be considered to identify a suitable subject population in which the product formulations will be the only significant determinants of bioequivalence[22].

## Drug dosing

In the bioequivalence studies of a generic product, a highest approved strength of the innovator product will be used unless there are safety concerns preventing the use of this strength[1, 3]. The dose administered should not be more than the recommended labeling instructions. For a single dose study US FDA recommends, test and reference products should not vary more than ± 5% in their potencies. The drug should be administered with sufficient fluid after at least 10 hours of fasting which is continued for at least 4 hours post-dose. To minimize the carry over effect a sufficient washout period should be scheduled between treatments[1]. Appropriate restrictions on fluid intake and physical activities should be maintained and all vital signs and adverse events are monitored post-dose.

To reduce the gastrointestinal side effects some drugs are given with food. Studies of such drugs should include studies with standard meals. The nature of the test meal to be administered-in the part of the study where the formulation is given in the presence of food-should be determined based on the physicochemical and pharmacokinetic characteristics of the drug and its formulation. The appropriate choice of the meal's timing and its contents should be chosen carefully[7, 9].

## Sampling schedules

The samples using appropriate biological matrix (blood, plasma, serum or urine) would be collected at different time periods from the participating subjects. The selection of these time points mainly depends on the pharmacokinetic behavior of the drug in the body[16, 17, 38]. Based on the in-vitro dissolution data using deconvolution method can help to determine the accurate sampling time points. Generally the biological matrix of choice is plasma or serum and if the measurement with these neither are nor reliable then urine may be analyzed. The trapezoidal rule is used on these sampling time points to estimate the area under the plasma concentration-time curve. After a single dose of administration, a rule of thumb is that blood samples are drawn at

several times during the absorption phase of the drug, then several times near the peak and at relatively fewer times in the elimination phase. Usually, 10-15 total sampling times are employed[27-29]. There are various designs published related to selection of appropriate sampling time points for individual and population pharmacokinetic studies. Increase in sampling time points may lead to concerns in ethical practices as this may lead to higher volume of blood draw, inconvenience due to number of vein punctures and compensation to the participating subjects[17].

## Moieties to be measured

In many cases the evaluation of bioequivalence would be based on the measured concentration of the parent compound[3]. The concentration-time profile of the parent compound is more sensitive to changes in formulation performance than a metabolite, which majorly reflects metabolism, distribution and elimination[1]. If the concentration of active compound is too low in the biological matrix and results in high variability or metabolite contributes significantly to safety and/or efficacy in those cases active or inactive metabolites of the compound can be measured. To understand the clinical pharmacology characteristics of a new drug it is always advisable to study the metabolite but this is still debated as it comes to the BE studies[30, 31]. If the metabolite significantly contributes to the total activity of an active substance and the pharmacokinetic system is nonlinear then both the parent and metabolite plasma concentrations should be measured separately. Eventually there are no specific regulatory guidelines which explain the requirements of submitting the metabolite data, but recommends that the sponsor should consult with the respective regulatory agency while preparing the protocol[16]. The complete statistical evaluation should be performed to the parent compound and the metabolite data can be used as a supportive evidence for comparing the therapeutic outcome[32].

## Bioanalytical methodology

Bioequivalence determination is purely dependent on the use of adequate analytical method used for the analysis of parent or metabolite[33, 35]. The reliability of the method used can be established by using different validation techniques. The validation demonstrates that the method used is appropriate for the intended purpose, i.e, qualitative, semi-quantitative or quantitative determination of drugs in the pharmaceutical formulations. US FDA has published a separate guideline on *Bioanalytical Method Validation* to assist sponsors in validating the bioanalytical methods[34]. Most of the regulatory bodies recommend that the methods used must be accurate, precise, specific, sensitive and reproducible. The analyst can modify the existing method as per the requirements but should be validated to ensure the performance. The validation procedures should be carried out using the same biological matrix for e.g. plasma to plasma or serum to serum. The stability procedures of samples should be studied and should reflect situations likely to be encountered during sample collection and analysis. It is recommended to select sufficient number of (~6 to 8) standards to correlate the relationship between concentration and response of the drug to be studied.

### Enantioselective bioanalytical methods:

During the drug development process the sponsor always choose to submit the data on racemic drugs instead of their constituent enantiomers. If the enantiomers differ in their

pharmacodynamic and pharmacokinetic properties as a result of stereo selective interaction with the biological molecules, the analyst should develop suitable method to identify the single safe and effective isomer[36-38]. Presently there is no regulatory precedence to address stereochemical aspects in bioequivalence studies, but there are only a few examples in the literature whereby the investigators have employed stereoselective assays in the bioequivalence testing of racemic drugs [39-41]. US FDA recommends measurement of individual enantiomer for bioavailability studies and for BE, measurement of racemates using an achiral assay would suffice. EMEA recommends BE studies of chiral active substance should be supported with enantiomeric bioanalytical methods. Japan has not issued any specific guideline on chiral drug development but recommends approaches mentioned in US FDA and EMEA guidelines.

**Pharmacokinetic & Statistical analysis**

The major concern in bioequivalence studies is to quantify the difference between the bioavailability of test and reference products and to ensure that they are not clinically different[3]. Generally majority of the regulatory bodies require both pharmacokinetic and statistical information on test and reference formulations under investigation[42-49]. The pharmacokinetic parameters obtained from plasma concentrations (e.g. Cmax and AUC) should be subjected to logarithmic transformation before analysis. The observed AUC (0-∞), Cmax or Tmax from the blood or plasma concentration-time is preferred because they provide the essential information about the pharmacokinetic characteristics in assessment of bioequivalence and are model independent and easy to calculate[2]. Various rules were proposed by FDA from 1977 to 1992 for testing the bioequivalence in terms of average bioavailability for specific drugs where the AUC and Cmax were the primary measures. Out of the several, only ±20 rule was acceptable by FDA for evaluation of average bioequivalence but sometime it may lead to inconsistent conclusions. Therefore the acceptable statistical method used for estimation of bioequivalence would be based on the 90% confidence interval (CI) for the parameters under consideration i.e. Cmax and AUC and should be in the limit of 80 to 125%. Except EMEA, no other regulatory agency has suggested the acceptance limits for narrow therapeutic or highly variable drug products. Interestingly, The Danish Medicines Agency considers that the bioequivalence acceptance limits for immunosuppressives must be within 90-111% as they are narrow therapeutic index drugs[50]. Most of the BE studies are designed to evaluate the average bioequivalence and therefore there are no specific recommendations for individual and population studies[51]. Considerable amount of debate is in progress for accepting the individual BE requirements proposed by FDA. The individual BE approach offers flexible equivalence criteria based on the individual therapeutic window and the variability of the reference drug product which is referred as 'subject to formulation interaction[2, 16, 42]. As there are several issues related to this concept, regulatory authorities need to explore before implementing as a guideline. FDA clearly states that if the predose concentration is more than 5% of Cmax, then the subject should be dropped from all the BE study evaluation[1]. There are no other regulatory except FDA which describes handling the data if there is vomiting reported for immediate and modified release dosage forms. There are several tests published for the detection of outlying data but there are no specific recommendations mentioned in the regulatory guidelines. Therefore reporting and handling of missing values and outliers should be described in the protocol. Few of the regulatory recommendations while designing and conducting a standard BE study are tabulated in Table 1,

**Table 1: Regulatory agency recommendations for bioequivalence study designs**

| Details | Regulatory Agency recommendations | | | | |
|---|---|---|---|---|---|
| | **US FDA** | **EMEA** | **TPD** | **ANVISA** | **CDSCO** |
| Number of subjects | Minimum 12 | Not less than 12 | Minimum 12 | Based on adequate statistical power | Not less than 16 |
| Design | Non replicate, Crossover, two treatment, two period, two sequence | Crossover, two treatment, two period, two sequence | Crossover, Two period | Non replicate, crossover, two treatment, two period, two sequence | Crossover, two treatment, two period, two sequence |
| Food effect study | Fast and fed studies are required for immediate and modified release dosage forms | Fasted studies for immediate release and both fasted and fed studies for modified release dosage forms | Fasted studies for immediate release and both fasted and fed studies for modified release dosage forms | Fasted studies for immediate release and both fasted and fed studies for modified release dosage forms | Fasted studies for immediate release and both fasted and fed studies for modified release dosage forms |
| Fasting status | Fasted for at least 10 hrs before drug administration | Fasting for at least during the night prior to dosing | Fasted for 10 hrs before dosing | Fasted for at least 8 hrs before drug administration | Fasted for at least 10 hrs before drug administration |
| Water intake | Allowed water as desired except for 1 hour before and after dosing.<br>240 mL water will be allowed during dosing. | At least 150 mL with dose. | 250 mL water permitted upto 2 hrs of dosing.<br>150 mL water with the dose. | Not specified | To be standardized and mentioned in the protocol. |
| Alcohol intake | Abstain from alcohol for 24 hrs | Should not have a history of alcohol | Should be mentioned in the | To be mentioned in the protocol | During the study and at least 48 hrs |

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| | before each study period and until after the last sample from each period is collected. | abuse. | protocol. | | before its commencement |
| Meals | Meals allowed no less than 4 hours after dosing | Not specified | Meals after 4 hrs of dosing | Not specified | Meals 4 hrs after dosing |
| Sampling schedule | Sampling at least three or more terminal half lives of the drug | Till adequate estimation of Cmax and AUC | At least three times the terminal half-life of the drug. | Equal to or higher than 3-5 times the elimination half-life of the drug or metabolite | At least 3 elimination half-lives |
| Washout period | Washout period at least 5 elimination half-lives | Washout period at least 3 elimination half-lives | Not less than 10 times the mean terminal half-life of the drug | Washout period at least 7 elimination half-lives | Washout period ≥ 5 elimination half-lives |
| Number of samples | 12 to 18 samples, including a predose sample, be collected per subject per dose. | Adequate estimation of Cmax & AUC | 12 to 18 samples should be collected per subject per dose | Predose and other sampling time points to be mentioned in protocol | Adequate estimation of total AUC |
| Steady state studies | Not required | Required, if the formulation is prolonged release or transdermal. | Required, if AUC ratio is less than 80% | Not recommended | Required on case to case basis |
| Observed AUC | % of AUC to be observed >88% | > 80% | > 80% | Not specified | Not specified |

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|---|---|---|---|---|---|
| Metabolite analysis | Required for drugs which form metabolite before or during absorption phase | Required for prodrugs or metabolite has significant efficacy | None | Required, if metabolite is active | Not specified |
| Statistical approach | Average BE | Average BE | Average BE | Average BE | Average BE |
| Pharmacokinetic parameters | AUCt, AUCinf, Cmax | AUCt, AUCinf, Cmax | AUCt, Cmax | AUCt, AUCinf, Cmax, Tmax | AUCt, AUCinf, Cmax, Tmax |
| Bioequivalence criteria | 90% CI between 80-125.00% | 90% CI between 80-125.00% | 90% CI between 80-125.00% | 90% CI between 80-125.00% | 90% CI between 80-125.00% |
| BE criteria for HVD | Not specified | Cmax 75-133% for HVD | Cmax-Add on studies are recommended | Not specified | Not specified |

US FDA: United States Food & Drug Administration
TPD: Therapeutic Products Directorate
CDSCO: Central Drugs Standard Control Organization
EMEA: European Medicines Agency
ANVISA: National Health Surveillance Agency

## Conclusions

As technology advances and regulations tighten, the competition to get new drugs on to the market has never been easy. The next few years look to be a critical time for the pharmaceutical industry as there is more number of challenges in generic portfolios. The development pipeline looks increasingly sparse, so equipping pharmaceutical business with cutting edge technologies and efficient strategies for drug development and reformulation will be the best way to keep profits high. The US FDA is also aiming to create an online database of bioequivalence study guidelines. This would be helpful to acquire information on designing bioequivalence studies for various types of drug products[57]. There are lot of other online forums available which discuss various scientific issues and requirements related to bioequivalence studies. Therefore countries should make an attempt to further strengthen their regulations clubbed with scientific discussions in providing safe and affordable drugs to the patients.

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