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Research article

Developments of bioequivalency regulations for orally administered pharmaceutical products in USA, India, and Gulf cooperation council states – Regulatory concept study

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Abstract

The concepts of bioequivalence have gained considerable importance during the last three decades because of their application to new brand-name drugs, as well as new generic drugs. Generic pharmaceutical products need to comply the same standards of quality, efficacy and safety of the innovator product. Generic product should be therapeutically equivalent and interchangeable with the reference product. Present study highlights the developments of bioequivalence regulatory requirements in USA, India and the Gulf Cooperation Council States (Saudi Arabia, Kuwait, The United Arab Emirates, Qatar, Bahrain, Oman and Yemen).

No international harmonization of regulatory requirements for bioequivalence, however, bioequivalence range and statistical analysis are to some extent harmonized, but there are differences in selection of subjects, selection of reference product, food effect, application of multiple dose study, in vitro dissolution study, etc. The growth of pharmaceutical market depends upon the drug regulatory system and drug regulatory laws. The drug regulatory system is responsible for protecting the public health by assuring the safety, efficacy and quality of human drugs and its distribution.

In generic drug approval process one of the major requirements is the bioequivalence study. In bioequivalence studies, the plasma concentration time curve is generally to assess the rate and extent of absorption. Selected pharmacokinetic parameters and preset acceptance limits allow the final decision on bioequivalence of the tested products. Present study includes recent developments and information about important aspects of bioequivalence study design and specification guidelines of each parameter.

Introduction

The responsibility of a regulatory body is to ensuring uniformity in standards of quality, efficacy and safety of pharmaceutical products. The study focus on the developments of bioequivalence regulatory requirements in the Gulf Cooperation Council states, India (CDSCO) and the United States of America. The comparison between the GCC, India (CDSCO) and USFDA regulatory requirements will be useful for pharmaceutical industry, those who are in the generic product development. Before going into bioequivalence studies it is essential for the pharmaceutical industry to study the guidelines of bioequivalence for the respective country where the industry wants to market its products and thus enter into generic market. It is encouraging to know that there are continuing efforts by regulatory authorities and the scientific community, both nationally and internationally, to understand and development more efficient and scientifically valid approaches.

The bioequivalence studies performed in one country are not acceptable by the other country. The specific BA/ BE study is required for each countries guidelines which results in waste of time, waste of resources, effective availability of the drug products in the market, duplication of efforts, delay in launch of the drug products.

Generic pharmaceutical products need to confirm to the same standards of quality, safety and efficacy of the originator's product. In addition, they should be clinically interchangeable with equivalent marketed products. To ensure interchange ability, the generic product must be therapeutically equivalent to the reference product. Many guidelines and regulations covering the licensing of generic products have been introduced to ensure that the medicinal products reaching the market have well-established efficacy and safety profile. To evaluate in the bioequivalence Pharmacokinetic parameters such as AUC_{0-t}, $AUC_{0-\infty}$, residual area, C_{max}, t_{max}, K_{el}, and $t_{1/2}$ are calculated. Importance of generic drugs in healthcare, it is

very vital that the pharmaceutical quality and in vivo performance of generic drugs be reliably assessed [1].

Bioequivalence focus on the release of a drug substance from its dosage form and subsequent absorption into systemic circulations. Due to harmonization of regulatory requirements for bioequivalence studies, major changes in policies and procedures concerning the determination of bioavailability and bioequivalence took place [2]. Saudi Arabia, Kuwait, The United Arab Emirates, Qatar, Bahrain, Oman and Yemen are the members of Gulf health ministers' council (GCC).

In bioequivalence documentation, formulation used in clinical trial and stability studies, the data needs to be assessed and the effect of temperature and humidity also are to be monitored. In pre study phase stability of a drug and its metabolites in the biological matrix under the condition of the experiment should be established. In oral solution stability of the active substance, should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference product.

In bio analytical method bench top stability, freeze thaw stability, stock stability should be monitored throughout the study.

Materials and methods

It is essential for the pharmaceutical industry to study the guidelines of bioequivalence for the respective country. The bio studies performed in any one country in this group is not fully acceptable by the other country. International Conference on Harmonization (ICH) finalized the concept of Pharmaceutical Quality System, providing a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product life cycle. A quality standard addressing the bio analytical testing of clinical trial samples would ensure consistency in the way of industry and organizations guideline. The format of the Bio analytical Quality Standard follows that provided by the ICH standard, providing guidance appropriate for a bio analytical laboratory. But in each country has their own guideline but all the guideline is related to ICH. In GCC countries following GCC guideline of bioequivalence [3]. GCC guidelines adherence to the EMA guidelines approaches to establish bioequivalence is almost similar and however in some aspects difference are there between both guidance. In USA USFDA has a strict guide line for the industries [4]. In India bioequivalence guide line are controlled by CDSCO [5]. The present study is planned to conduct comparative evaluation and recent research and developments of bioequivalence regulations for the generic drugs in detail to test the hypothesis of the regulations. The structure approach will be followed for research. Bioequivalence study intended to look at the in vivo execution of a test pharmaceutical item contrasted with reference pharmaceutical product [6]. The methodology may include interviews, surveys and other quantitative or qualitative techniques, and could include both present and historical information.

1. Study design:

To list out the regulation of each country to compare the regulatory point was to discuss the variation and similarities. The study will be executed in 3 Phases:

1.1. Phase 1: Data collection on bioequivalence Regulation in USA, GCC and India.

This will begin with Identification of the latest regulation on bioequivalence studies required in USA, GCC & India. This will be executed with the help of internet, public libraries, industrialist consultation and pharma regulatory specialists. The aim will be to collect all Government Regulations, blog and articles pertaining to bioequivalence studies in USA, India and GCC.

1.2. Phase 2: Desk and Field Research

This will begin study the recent update of regulation and evaluate similarities and differences in regulations. Once the data is ready and verified it with interpret in terms of similarity and differences. The basic presentation of data will require the tabular listing of the regulation and response by the experts.

1.3. Phase 3: Final Report and Presentations

Final report will test the recent development and similarities and difference and recommendations presented in tabular format.

Following pharmacokinetic parameters should be calculated from plasma concentrations of the drug /metabolites AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, C_{min}, T_{max}, $t_{1/2}$ and K_{el} in bioequivalence study. Present study highlights the relevant regulatory guidelines and different study design and specification also been addressed [7].

Study is performed with following considerations:

1. BE studies authorization procedure by Ministry of health/FDA with respective countries
2. Approval of ethical committee
3. Selection of subjects /reference product/ test products
4. Number of subjects required
5. Informed consent procedures
6. Dietary restrictions during the study
7. Drug administration Procedure
8. Selection of dose for each volunteer
9. Method of administration of drug product to volunteers
10. Blood/urine Sampling schedule and procedure for studying absorption pattern
11. Substances to be measured in biological fluids
12. Selection and validation of analytical methods for estimating absorbed drug

13. Washout period between the studies
14. Procedure for data recording and presentation
15. Procedures for statistical analysis of results
16. Procedures for data interpretation
17. Rules for acceptance criteria of BE criteria
18. Signatories for the final report
19. Regulations for reporting the results to health authorities
20. Regulations to compensate the volunteers for health hazards if incurred during the studies
21. Regulatory actions for falsifying the studies/reports
22. Licensing, de licensing and relicensing procedures for BE centers
23. Regulatory audit procedures for BE centers
24. Regulations for establishing validity of analytical methods
25. Official Formats for licensing/conducting/reporting BE studies
26. Data archiving procedure.

Results and discussion

Regulatory guidelines are necessary to standardize the evaluation procedure in bioequivalence. Present research covers major aspect of the development and requirement of bioequivalence study along with the regulatory specification of these three regions. Harmonization of regulatory requirements for bioequivalence studies, major changes in policies and procedures concerning the determination of bioavailability and bioequivalence took place. Therefore in the near future one may expect appropriate choice of a clinically relevant bioequivalence range based on therapeutic ranges, absorption profile and ultimately experimental design to resolve the issue of intra and inter subject variability. It describes the important differences and similarities in BE approaches for the regulatory agencies of USA, India and GCC, Moreover, it briefly compares and given the prompt overview of the bioequivalence study requirements in these region.

No	Criteria	USA (USFDA)	India (CDSCO)	Gulf Cooperation Council. Executive Board of The Health Ministers Council For GCC States.
1.	Type Reference product	The reference product can be the only Reference List Drugs listed in Orange Book.	The reference product can be the global innovator product. Some cases, CDSCO or DCGI has designated specific brands to be used.	The reference Product must be the original brand-name. (Manufactured in the country of origin with the original brand name).
2.	Source of Reference product	The reference product needs to be sourced only from the US Market.	Any market.	Reference Products must be the original brand-name (i.e. manufactured in the country of origin. If this is not available in the market then the brand name regarding the same company but different country of origin is used, or marketed in ICH region, GCC region, or in any stringent regulatory authority [3].
3.	Substitute Reference product	Reference product has been withdrawn from market, one of the generic products listed in Orange Book, be selected as the reference product.	The recommended reference product is not available in the market or no longer produced. Preapproved Indian brands may be used as reference products.	If the recommended reference product is not available in the market or no longer produced, then the product which is the local market leader may be used as a reference product.
4.	Test Product	The test product used in the study should be representing the product to be marketed. The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified. The batch production should provide a high level of assurance that the product and	The test product used in the study should be representative of the product to be marketed. The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified.	The test product used in the study should be representing the product to be marketed. The test product should usually originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater, unless otherwise justified. The batch production should provide a high level of assurance that the product and process will be feasible on an industrial scale.

		process will be feasible on an industrial scale [4].		
5.	Selection of Subjects	The total number of subjects in a study should be sufficient to provide adequate statistical power for BE demonstration. (Earlier guidance sample size requires 12 subjects).	Normal 16 healthy Subjects.	Normal 24 healthy subjects, A number of subjects of less than 24 may be accepted (with a minimum of 18 subjects) when statistically justifiable. preferably nonsmoking, between 18-55 years in age and within 15% of ideal body weight.
6.	Gender	Male and/or female	Male and/or female.	Male and/or female
7.	Age	Subjects be 18 years or older.	Adult healthy volunteers	Subject be between 18 - 55 years.
8.	BMI	USFDA does not make recommendations regarding BMI.	Not specified	BMI be between 18.5 – 30 kg/Sq.m. [3].
9.	Fasting Study	At least 10 hours of fasting which is continued for at least 4 hours post-dose.	Overnight fasting of 10 hours with subsequent fasting of 4 hours post dose	Subjects fast for at least 8 hours prior to administration of the products, unless otherwise justified.
10	Fed Study	Food effect BA studies are usually conducted for new drugs and drug products during the food on the rate and extent of absorption of a drug when the drug is administered shortly after a meal (fed conditions), as compared to administration under fasting conditions.	For the products which are recommended to be taken along with meal. Fed studies may also be required for modified release drugs in addition to fasting studies	For products where the SPC recommends intake of the reference medicinal product in fed state only.
11	Diarrhea/ Emesis/ Vomiting	USFDA recommends that the data from subjects who experience emesis during the course of BE study for immediate release. Products are deleted from statistical analysis if vomiting occurs. In case of modified release products, data from subjects who experience emesis / diarrhea any time during the labeled dosing interval should be deleted.	There have been no recommendations provided.	Examples of the reasons to exclude results from a subject in a particular period are events such as vomiting and diarrhea which could render the plasma concentration time profile unreliable. In exceptional cases, the use of concomitant medication could be a reason for excluding a subject.
12	Replacement of subjects withdrawal or dropout Special considerations	There are as such no provisions provided by USFDA regarding the replacement of subjects on dropouts or withdrawals.	It is acceptable to replace a subject withdrawn/ dropout from the study once it has begun, provided that the substitute follows the same protocol originally intended for the withdrawn subject and he/she is tested under similar environmental and other controlled conditions	Sponsors should enter a sufficient number of subjects in the study to allow for dropouts. As replacement of subjects could complicate the statistical model and analysis, dropouts should not be replaced generally.
13	Physical Activity	USFDA does not provide any guidance on the posture or physical activity.	Recommends standardization of study Environment, involving the post-dosing postures.	Posture and physical activity may need to be standardized. No any special guidelines.
14	Water/Fluid Intake	USFDA, the test or reference products can be administered with about 8 ounces (240 ml) of water under fasting conditions, unless the study is a food-effect bioequivalence	CDSCO recommends on standardization of the fluid intake in all studies.	It is recommended that water is allowed as desired except for one hour before and one hour after drug administration. Test and reference products should be administered standardized volume of 150 ml water.

		study. The subjects are allowed water as desired except for one hour before and one hour after the drug administration.		
15	Subject replacements on dropout or withdrawal	Not Specified.	No special guideline	No replacements.
16	Wash-out period	According to USFDA, an adequate washout period (e.g. more than 5 half-lives of the moieties to be measured) should separate depending the treatment.	Doesn't provide any recommendation on the washout period	GCC Recommends sufficient washout period during crossover studies. Normally at least 5 elimination longest half lived.
17	Sampling	USFDA recommends that 12-18 samples, including the pre dose sample, should be collected per dose per subject. Sampling can be continued for at least three or more terminal half-lives of the drug. It recommends withdrawal of the samples at appropriate times to describe the absorption, distribution and elimination phases of the drug.	Furthermore, there should be at least three sampling points during the absorption phase, three to four at the projected T, and four points during the elimination phase.	A sufficient number of samples to adequately describe the plasma concentration-time profile are collected. The sampling schedule should include frequent sampling around predicted T_{max} to provide a reliable estimate of peak exposure.
18	Food specification for fed studies	High fat approximately 50 percent of total caloric content of the meal and high-calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively.	Consumption of a high-fat breakfast before dosing recommended. Such a breakfast must be designed to provide 950-1000 Kcals At least 50% of these calories must come from fat, 15-20% from proteins and the rest from carbohydrates.	The composition of the meal is recommended to be according to the SPC of the originator product. If no specific recommendation is given in the originator SPC, the meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively.
19	Withdrawal quantity of blood	Not Specified.	Not specified.	Not specified.
20	Strength of the dosage form	According to USFDA, for the drug product with different strengths, in vivo BE demonstration of one or more lower strengths can be waived based on dissolution tests and in vivo study on the highest strength. However, in few cases conducting the study on not the highest strength may be appropriate for reasons of safety, provided that the following conditions are met. (a) Linear elimination kinetics has shown over the therapeutic dose range. (b) The higher strengths of the test and reference products are	According to CDSCO, single dose studies are generally recommended. However, there are some situations where the steady study design is required such as: (a) Drugs with dose and time dependent pharmacokinetics. (b) Some modified release products. (c) When there is a problem of sensitivity in plasma concentration measurements after the single dose administration. (d) If the intra-individual variability is reduced at the	If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the various strengths. Biowaiver applicable when the active substance(s) in test and reference products are identical. Biowaiver may also be applicable if test and reference contain different salts provided that both belong to BCS-class I.

		proportionally similar to their corresponding lower strength. (c) Comparative dissolution testing on the higher strength of the test and reference products is submitted and found to be appropriate.[4] (As per BCS classification) USFDA accepted biowaiver application only BCS class 1 drugs. But supportive biowaiver criteria with scientifically justified BCS class 3 also accepting.	steady state. In India biowaiver application is applicable only BCS class1 drugs.	
21	Strength to be investigated Linear Pharmacokinetic	If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one strength. (Generally highest strength).	Not specified.	If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths, depending on the proportionality in composition between the different strengths. (Generally highest strength).
22	Study pattern Immediate release and modified release drugs with moderate half life	Single dose, randomized, 2-Period, 2- treatment, crossover study. The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of Bio analytical quantification in all subjects at the beginning of the second period.	Single dose, randomized, 2-Period, 2- treatment, crossover study.	Single dose, randomized, 2-Period, 2-treatment, crossover study.
23	Study pattern Immediate release and modified release drugs with long half-life drugs.	Single dose, non-replicate cross over designs with adequate washout period is used. If the crossover study is problematic, a BE study with a parallel design be used.	Single dose, non-replicate cross over designs with adequate washout period is used. If the crossover study is problematic, a BE study with a parallel design can be used.	No specific guideline. (Parallel design)
24	Study pattern Immediate release and modified release drugs Highly variable drugs	Single dose, non-replicate cross over designs with adequate washout period is used. If the crossover study is problematic, BE study with a parallel design be used.	Single dose, non-replicate cross over designs with adequate washout period is used. If the crossover study is problematic, a BE study with a parallel design can be used.	No specific guideline. (Replicate design)
25	Study pattern Multiple dose formulation	Multi dose study if necessary.	The multiple dose Studies are advocated when required.	A multiple-dose study may be required Drugs with dose and time dependent pharmacokinetics. Some modified release products. If a problem of sensitivity in plasma concentration measurements after the singledose administration is noticed.
26	Parameters to be measured	AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, λz, and $t_{1/2.}$	AUC_{0-t}, $AUC_{0-\infty}$, $C_{max,}$ T_{max}, λz, and $t_{1/2.}$	AUC_{0-t}, $AUC_{0-\infty}$, $C_{max,}$ T_{max}, λz, and $t_{1/2.}$
27	Acceptance Normal drugs	It is based on being identical in dose, strength, route of administration, safety, efficacy, and intended use.	It is based on being identical in dose, strength, route of administration, and blood levels Pharmacodynamics or	It is based on the extent and rate of absorption after administration in the same molar dose lie within acceptable predefined limits. These

		The pharmacokinetic and Pharmacodynamics properties of Reference Product and Generic Product shall be identical when administered at the same molar ratio The FDA's use of the word identical is very much a legal interpretation, and is not literal. C_{max} 80-125% AUC_{0-t} 80-125% $AUC_{0-\infty}$ 80-125%	clinical endpoints are considered only if needed. There is no consideration for intended use. The extent and rate of absorption of Comparator Product and Generic Product shall not be significantly different from each other when analyzed statistically and when administered at the same molar dose. [5] C_{max} % 80-125 AUC_{0-t} % 80-125 $AUC_{0-\infty}$ % 80-125	limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy.[3] C_{max} % 80-125 AUC_{0-t} % 80-125 $AUC_{0-\infty}$ % 80-125
28	Acceptance Narrow therapeutic drug	C_{max} 80-125% AUC_{0-t} 80-125%	Acceptance criteria not defined	C_{max} 90 to111 AUC_{0-t} 90 to111
29	Acceptance Highly variable drugs	C_{max} (80 -125) % GMR (80 -125) %	Acceptance criteria not defined	C_{max} 75-133 GMR 80 to 125%
30	Other requirements Genetic Phenotyping/ Genotyping	USFDA does not provide any information on the genetic Phenotyping/Genotyping. Indicates these studies only for early clinical trials.	Phenotyping and/ or genotyping of subjects should be considered for exploratory bioavailability studies and all studies using parallel group design. It may also be considered in case of cross-over study designs for safety or pharmacokinetic reasons. Furthermore, if a drug is known to show altered pharmacokinetic profile due to major genetic polymorphism, studies could be performed in panels of subjects of known phenotype or genotype for the polymorphism in question.	Phenotyping and/or genotyping of subjects be considered for safety or Pharmacokinetic reasons.
31	Drug/ Metabolite	USFDA recommends the measurement of the parent drug released from the dosage form, rather than the metabolite because the concentration time-profile of the parent drug is more sensitive to changes in formulation performance than the metabolite, which is more reflective of the metabolite formation, distribution and elimination. However, there are few exceptions where the measurement of metabolite becomes important, for instance, the measurement of a metabolite may be preferred when the parent drug levels are too low to allow reliable analytical measurement in	The use of parent drug data to estimate BE. However, their opinions and justifications for the use of metabolites as a primary data are different. CDSCO recommends on measuring the active drug substance as the main evaluation criteria for BE, however, in some cases where the concentrations of the drug (s) may be too low to be accurately measured in the biological matrix or in case of the unstable drugs or drugs with the short half-lives or pro-drugs, measurement of the active main metabolite is considered for the evaluation	In principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound. The reason for this is that C_{max} of a parent compound is usually more sensitive to detect differences between formulations in absorption rate than C_{max} of a metabolite.

		blood, plasma or serum for an adequate length of time or if the active metabolite may be formed as a result of gut wall or other pre systemic metabolism. Therefore, if the metabolite contributes meaningfully to safety and/or efficacy, the measurement of Metabolite and the parent drug is recommended.	purpose.	
32	Statistical evaluation	USFDA recommends on providing information regarding AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, λz and $t_{1/2}$. If the steady state studies are employed, C_{min}, $C_{av½}$, degree of fluctuation and swing are employed.	Confidence interval for the ratio of geometric means of AUC (for both AUC and AUC_{0-t}) and C determined using log-transformed data should generally be within the range of 80 to 125%, when the products are compared after single dose administration in both the fasting and fed state [5].	Statistical analysis is recommended. 90%confidence intervals for the ratio of the population geometric means (test / reference) for the parameters under consideration. The ANOVA tables, including the appropriate statistical tests of all effects in the model, should be submitted.
33	GMP requirements for bioequivalence center	USFDA recommendation	CDSCO recommendations	As per GCC guidelines
34	Countries applicable	United States of America.	India	Bahrain, Saudi Arabia, The United Arab Emirates, Kuwait, Qatar, Oman and Yemen.

Conclusion

Harmonization of regulatory requirements for bioequivalence major changes required in policies and procedures. Major differences in the regulatory framework can be observed in the types of clinical designs, the treatment of highly variable drugs, the potential for granting a biowaiver based on BCS, the types of pharmacokinetics parameters used, metabolite data, enantiomers, and endogenous substances. Past-2010 period some emerging issues have risen like phenotyping /genotyping in BE studies, the evaluation of super generics, and the important role of modeling and simulation in assessment. Regulatory authorities develop the new regulatory concepts and requirements to regulate the quality of the product [8]. Near future one may expect appropriate choice of a clinically relevant bioequivalence based on therapeutic ranges, absorption profile and ultimately experimental design to resolve the issue of intra and inter subject variability. Present research study will provide an easy quick overview for regulatory consideration required for bioequivalence study.

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