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An Overview on Bioequivalence Regulatory Requirements of Pharmaceutical Products: India and Gulf Cooperation Council States - (Gulf Cooperation Council Guidelines)

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Abstract

Generic pharmaceutical products need to comply the same standards of quality, efficacy and safety as required of the innovator product. Generic drug market is expected to rise in coming future. Specifically, the Generic product should be therapeutically equivalent and interchangeable with the reference product. Present study highlights the regulatory guidelines for conduct of bioequivalence in India and the Gulf Cooperation Council States.

There is 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, food effect, application of multiple dose study, in vitro dissolution study, reference product etc.

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. (AUC) the area under the concentration time curve reflects the extent of exposure. (C max) the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, (t max) are parameters that are influenced by absorption rate.

Bioequivalence study is one of the main requirements for generic drug approval process. This review provides an easy and quick overview for regulatory consideration required for bioequivalence study in those regions. In this paper includes information about important aspects of bioequivalence study design and specifications guidelines of each parameters also have been addressed.

Keywords*: Bioequivalence, Bioavailability, Pharmacokinetics, GCC (Gulf Cooperation Council).*

Introduction

No country in the world is able to manufacture all the medicinal products at all the times. Imports of medicines especially tablets/capsules are mandatory to cover shortages at times. Each country has its own regulatory system to check the quality, safety and efficacy of the imported drug products. One of the most critical quality parameters for Tablets and Capsules is the Bioavailability and Bioequivalence i.e. the rate/extent of absorption of the drug on ingestion.[1]

Unlike most of the laboratory studies, BA/BE studies are quite tedious, tightly controlled and expensive. The studies require a pool of healthy volunteers, a well-designed analytical laboratory, sophisticated instrument, expert analysts, statistician, medical experts, patient housing area and much more [2, 5]. Last two decade, due to expiry of patented products as well as their exclusivity period, a drastic up streaming of generic drug market has been observed in developed as well as developing nations.

The standards for BE studies vary from country to country with respect to the followings[3].

1. Number of volunteers required for the study
2. Selection criteria,
3. Informed consent procedures,
4. Appointment of Ethical committee
5. Physical fitness of volunteers before the study,
6. Dietary restrictions during the study
7. Dosing of the drug
8. Drawing of blood samples for analysis

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9. Method of analysis
10. Validation of Analytical Methods
11. Actual analysis
12. Data integrity
13. Presentation of data
14. Calculation of BA/BE data pharmacokinetic parameters
15. Data documentation
16. Final review and conclusion
17. Limitation of the studies
18. Management of untoward effects during the studies

The regulations for bio studies in GCC (Gulf) and India are grossly inconsistent and non-inter-exchangeable. The bio studies performed in any one country in this group is not fully acceptable by the other country [6].

Method

The literature required for the thesis was sourced from regulations imposed by India and GCC. In addition, books and scholarly articles published by BA/BE Experts were studied [4]. Even personal discussions and meetings were held with experts. Bioequivalence study intended to look at the in vivo execution of a test pharmaceutical item contrasted with reference item [13]. This study looks into the requirements of bioequivalence with study parameters

Such as study design, fasting or fed state studies, volunteers' recruitment, study dose, sampling points, analytical method validation parameters, pharmacokinetic parameters, criteria for bioequivalence, GCP requirements etc, which are needed for the pharmaceutical industry to carry out bioequivalence studies and to file ANDA. The following methods were adopted for data collection:

Literature Review

Personal interview

Panel discussion

The structural approach, followed by collecting and verifying the data [7, 8].

1. Type of the Tablets/Capsules for which studies are mandatory
2. Type of the Tablets/capsules for which the studies are not required
3. Selection of comparator/test product for the studies
4. No of volunteers required for each study
5. Inclusion/Exclusion Criteria for the studies
6. Demographic requirements during the study
7. Classification of the products for the studies
8. Methodology for conducting the study
9. Recording and statistical evaluation of study data
10. Acceptance criteria

Result and discussion

Bioequivalence study is one of the major parameters in drug approval in generic medicines. This research covers major aspect of requirement of bioequivalence study along with the regulatory specification of various countries. Recommendations for improvements in current BE guideline on certain aspects like general study design, blinding, gender, of subjects, replacements of subjects on withdrawal or dropout's genetic phenol typing respectively have been made. A comparative difference in study design and specifications have also been address. The following parameters of the study were compared to check the hypothesis.

No	Criteria	India	GCC
1.	**Reference product Type**	The reference product can be the global innovator product. In some cases, DCGI has designated specific brands to be used as comparator Product	The reference Product must be the original brand-name (Manufactured in the country of origin of the original brand name)

2.	**Reference product Source**	The reference product can be sourced from any market	The reference product can be sourced from any market
3.	**Reference product Substitute**	If 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 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 production of batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale	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 production of batches used should provide a high level of assurance that the product and process will be feasible on an industrial scale.
5.	**Subjects**	16 Healthy Subjects	24 normal healthy subjects, preferably nons moking, between 18-55 years in age and within 15% of ideal body weight.
6.	**Type of study Immediate release and modified release drugs with Moderate half-life**	Single dose, non-replicate cross over designs are recommended	Normally, Single dose crossover study in fasting state is required.
7.	**Strength to be investigated Linear Pharmacokinetics**	If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one strength (generally highest), depending on the proportionality in composition between the different strengths	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
8.	**Strength to be investigated Linear Pharmacokinetics**	If several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one strength (generally highest), depending on the proportionality in composition between the different strengths	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
9.	**Study pattern Immediate release and modified release drugs with moderate half**	Single dose, randomized, 2-Period, 2- treatment, crossover study.	Single dose, randomized, 2-Period, 2- treatment, crossover study.

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	life		
10.	**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 can be used.	No specific guideline.
11.	**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, a BE study with a parallel design can be used.	No specific guideline.
12.	**Study pattern Multiple dose formulation**	The multiple dose Studies are advocated when required[13, 14].	A multiple-dose study may be required Drugs with dose and time dependent pharmacokinetics. Some modified release products. When there is a problem of sensitivity in plasma concentration measurements after the single dose administration.
13.	**Fasting**	Overnight fasting of 10 hours with subsequent fasting of 4 hours post dose	At least 10 hours of fasting is recommended
14.	**Fed Study**	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 only in fed state, the bioequivalence study should generally be conducted under fed conditions.
15.	**Acceptance Normal drugs**	It is based on being identical in dose, strength, route of administration, and blood levels Pharmacodynamics or 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 C_{max} % 80-125 AUC_{0-t} % 80-125 $AUC_{0-¥}$ % 80-125	It is based on the extent and rate of absorption after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e. similarity in terms of safety and efficacy C_{max} % 80-125 AUC_{0-t} % 80-125 $AUC_{0-¥}$ % 80-125

16.	**Acceptance Narrow therapeutic drug**	Acceptance criteria Not defined	C_{max} 90 to111 AUC_{0-t} 90 to111
17.	**Acceptance Highly variable drugs**	Acceptance criteria Not defined	C_{max} 75-133 GMR 80 to 125%
18.	**Other requirements Age**	The subjects to be recruited for in vivo BE studies healthy adult volunteers having 18 to 55 years.	Subjects should be 18-55 years of age
19.	**Other requirements BMI**	DCGI does not make any recommendations regarding BMI (However, BMI @ 18.5 to 25 kg/m2 are recommended.	**BMI s**hall be 18.5 and 30 kg/Sq.m. GCC Guideline for BE 2.4.
20.	**Other requirements Genetic Phenotyping**	As per CDSCO, the 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 (CDSCO, 2005).	Phenotyping and/or genotyping of subjects may be considered for safety or Pharmaco-kinetic reasons.
21.	**Parent drug/Metabolite**	The CDSCO suggest 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,	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.

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		measurement of the active main metabolite is considered for the evaluation purpose.	
22.	**Posture and Physical Activity**	CDSCO recommends standardization of study Environment, involving the post-dosing postures.	As the bioavailability of an active moiety from a dosage form could be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardized.
23.	**Emesis/Vomiting**	There have been no recommendations provided.	Examples of reasons to exclude the results from a subject in a particular period are events such as vomiting and diarrhoea 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
24.	**Fasting conditions**	According to CDSCO guidelines, a single dose study should be conducted on overnight fasted subjects with a minimum fasting period of 10 hours and post dose fasting of 4 hours. In case of multiple dose studies, where an evening dose is also scheduled, 2 hours of fasting before and after the dose is considered.	In general, a bioequivalence study should be conducted under fasting conditions
25.	**Food specification for fed studies**	CDSCO recommends the consumption of a high-fat breakfast before dosing. 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. Furthermore, the vast ethnic and cultural variations of the Indian subcontinent preclude the recommendations on consumption of any single standard high-fat breakfast 15 minutes before dosing. A high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal should derive approximately 150, 250 and 500-600 kilocalories from proteins, carbohydrates and fats	No food is allowed for at least 4 hours post-dose. Meals taken after dosing should be standardized in regard to composition and time of administration during an adequate period of time. Food specifications not provided for fed studies

		respectively (CDSCO, 2005) [15].	
26.	**Fluid Intake**	CDSCO recommends on standardization of the fluid intake in all studies (CDSCO, 2005).	It is recommended that water is allowed as desired except for one hour before and one hour after drug administration
27.	**Sampling**	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 (CDSCO, 2005).	A sufficient number of samples to adequately describe the plasma concentration-time profile should be collected. The sampling schedule should include frequent sampling around predicted t_{max} to provide a reliable estimate of peak exposure
28.	**Wash-out period**	CDSCO doesn't provide any recommendation on the washout period	GCC Recommends sufficient washout period during crossover studies
29.	**Statistical Data**	As per CDSCO, the confidence interval for the ratio of geometric means of AUC (for both AUC and AUC0-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 (CDSCO, 2005).	Statistical analysis is recommended
30.	**Strength of the dosage form**	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 steady state (CDSCO, 2005).	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.
31.	**Special considerations Replacement of subjects Withdrawal or dropout**	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	Sponsors should enter a sufficient number of subjects in the study to allow for dropouts. Because replacement of subjects could complicate the statistical model and analysis, dropouts generally should not be replaced.[11, 12]

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		environmental and other controlled conditions [9, 10]. (CDSCO 2005).	

Conclusion

In this study provide quick overview for regulatory considerations required for bioequivalence study. It provides an easy quick overview for Regulatory consideration required for bioequivalence study in different countries. This review covers major aspect of requirement of bioequivalence study along with the regulatory specification of various countries. There are several parameters which can be considered to draw harmonized guidelines which will be good enough for all the two regions and will rule out duplication of studies.

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