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Comparison of Regulatory Aspects for the Conduct of Bioavailability and Bioequivalence Studies

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ABSTRACT

The widely used regulatory guidelines in India were identified which mentions the regulatory requirement for the conduct of bioavailability and bioequivalence studies by the respective regulatory authorities. This comparison involves comparing six widely used regulatory guidelines such as FDA (Food and Drug Administration, USA), EMEA (European Agency for the evaluation of Medicinal Products, Europe), ANVISA (National Health Surveillance Agency Brazil), CDSCO (Central Drugs Standard Control Organization, India), WHO (World health Organization) and presenting them in a common platform which enables uncomplicated understanding. The regulatory guidelines were compared on the basis of various parameters involving the clinical conduct of the bioavailability and bioequivalence studies. The comparison made is of benefit to fraternity in Clinical Research Organization and Pharmaceutical Industry as it aids them in understanding the conduct of such studies mentioned in the guidelines in a common platform, this will aid them in conducting the studies according to the requirements of the respective guidelines for the country they filling the ANDA. The comparison is also of benefit to the academic fraternity as it will open a new arena for understanding the regulatory aspects of the conduct of the bioavailability and bioequivalence studies. This opens a window in the common platform of clinical as well as regulatory aspects of bioavailability and bioequivalence studies.

KEY WORDS: Bioavailability, Bioequivalence, FDA, ANVISA, CDSCO, WHO

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INTRODUCTION

Pharmaceutical companies are now a days immensely competitive and are spending billions of rupees in the new drug development process. However, the success rate is very less. Therefore, most of the companies are in conquest of the generic market; Generics are not required to repeat the extensive clinical trials used in the development of the original, brand-name drug. Instead, generics must show they are bioequivalent to the pioneer (Innovator product) drug and fall into acceptable parameters for bioavailability, or the extent and rate at which the body absorbs the drug. With escalating pressures on research and development (R&D) and cost-containment across the global pharmaceutical industry, there is increased focus on reducing the costs of clinical development, which comprises two-thirds of development costs. The additional problem of delayed development time is also affecting introduction of new drugs, losing incremental revenues. One of the major factors for this delay is unsatisfactory patient recruitment rates. This dual challenge of accelerating clinical development and reducing costs has forced major pharmaceutical companies to look at alternative destinations such as India for sourcing patients for their global studies [1].

CURRENT SCENARIO

In recent times, Bioavailability and Bioequivalence studies is of interest to all in the fraternity of Pharmaceutical and Medical Sciences. With India as an emerging hub of conduct of such generic studies, it is of paramount importance that the regulatory requirements for the conduct of the bioavailability and bioequivalence studies mentioned in the widely prevailing guidelines of the respective regulatory authorities are understood. In India, currently lots of outsourcing for bioavailability and bioequivalence studies are being carried on. Clinical Research Organization and Pharmaceutical companies are conducting bioavailability and bioequivalence studies for ANDA submission to regulatory authorities such as FDA (USA), EMEA (Europe), ANVISA (Brazil), CDSCO (India), TGA (Australia) etc. The requirements mentioned in the guidelines for conduct of such studies by these regulatory authorities vary. If the bioavailability and bioequivalence study is not conducted according to the requirements, obtaining an approval for the generic drug becomes difficult.The

regulatory requirements for conduct of bioavailability-bioequivalence studies are not uniform across the globe. It is very complicated and perplexing to ensure that all the requirements for submission of bioavailability-bioequivalence studies to different regulatory authorities have been satisfied as the requirements differ from country to country. Thus, it is necessary that all the regulatory guidelines for bioavailability-bioequivalence studies, authorized by the regulatory authorities of various countries are compared and all the differences in the same are present in a common platform.

Table1: Comparison of the regulatory requirement for the conduct of the bioavailability and bioequivalence studies mentioned in guidelines of India, United States of America and Europe

PARAMETER	CDSCO	FDA	EMEA
Name of the Organization	Central Drugs Standard Control Organization	Food and Drug Administration	European Agency for the evaluation of Medicinal Products
Country Representing	India	United States of America	Europe
Guideline	Guidelines for Bioavailability & Bioequivalence Studies(March,2005) [2]	1. Guidance for Industry-Bioavailability and Bioequivalence Studies for orally administered drug products-General Considerations (March, 2003) [3] 2. Guidance for Industry-Food-Effect Bioavailability and Fed Bioequivalence Studies (December,2002) [4]	Note for Guidance on the investigation of Bioavailability and Bioequivalence (July,2001) [5]
Study Design **1.General**	Single dose, randomized, 2-Period, 2- treatment, cross-over study design.	Single dose, cross-over study for fasted and fed states.	Single dose, cross-over study for fasted and fed states.
2.Long half life drugs	Parallel design.	Non replicate single dose crossover/parallel study with adequate washout period.	Relative BA can be adequately estimated using truncated AUC.
3.Highly variable drugs	Replicate Study design.	Replicate study design.	Steady state or replicate Study design.

Sample Size	Healthy Volunteers, Not less than 16 unless justified for ethical reasons.	Healthy Volunteers, N>12	Healthy Volunteers, N>12 Min. No. of volunteer's should be not less than 12 unless justified.
Replacement of subjects on withdrawal or dropout	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 the subject is tested under similar controlled conditions.	Not specified	Not specified
Gender of the Subject	Male/female; the choice of gender should be consistent with usage and safety criteria. If drug product is intended for use in both sexes, attempt should be made to include similar proportions of females and males in the study.	Male/female; If drug product is intended for use in both sexes, attempt should be made to include similar proportions of females and males in the study	Male/female
Female Subjects	Women taking contraceptive drugs should normally not be included in the studies.	Not specified	Not specified
Age criteria	≥ 18 years; If the drug product is intended for use in elderly, attempt should be made to include as many subjects of 60 years of age or older.	More than 18 yrs	18-55years
BMI	Not specified although it is mentioned that studies to be performed on healthy volunteers.	Not specified	Normal values
History of Smoking Criteria for Selection of Subjects	Not specified	Not Specified	Preferable non-smokers or in case moderate smokers <10 cig per day, then these should be identified.

PARAMETER	CDSCO	FDA	EMEA
History of Alcohol and Drug Abuse Criteria for Selection of Subjects	Not specified	Not Specified	Without any History of Alcohol and Drug abuse.
Restrictions (Smoking/Alcohol and Drug Abuse)	Unless the study design requires, subjects should abstain from smoking, drinking alcohol/coffee/tea/xanthine containing foods & beverages, fruit juices during the study and at least 48 hours before its commencement.	Subjects should Abstain from alcohol for 24 hours prior to each study period and until after the last sample from each period is collected.	The subject should not take other medicines during a suitable period before and during the study and should abstain from food and drinks, which may interact with circulatory, gastrointestinal, liver or renal function(e.g.- alcoholic, xanthine containing beverages or certain fruit juices).
Fasting prior to study	**Single dose**: At least 10 hrs overnight and 4 hrs after dosing. **Multiple dose**: 2 hr before and after dose.	10 hrs before and 2 hrs after drug administration.	At least during night prior to drug administration.
Food Specification for Fed Studies	Requires consumption of a high-fat breakfast approx 15 mins before dosing(950-1000KCalories){50% of Calories–Fat;15-20% of Calories-Proteins; Rest Carbohydrates}.	A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal for Food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.	Not Specified

PARAMETER	CDSCO	FDA	EMEA
No. of Samples	Duration of at least 3 elimination half lives. There should be at least 3 sampling points during the absorption phase,3-4 at the projected Tmax & 4 points during the elimination phase. Incase of measurement of Urinary Excretion, it is necessary to collect urine for 7 or more half lives.	12-18 samples including predose sample per subject per dose, duration of at least 3 or more elimination half life of drug/metabolite.	3-4 samples during terminal log linear phase.
Water Restriction	Not Specified	Prior to and during each Study phase, subjects should be allowed water as desired except 1 hr before and after drug administration.	Not Specified
Subjects with Pre-dose plasma conc.	Not Specified	If the Pre-Dose concentration is less than or equal to 5 percent of Cmax value in that subject, the subject's data without any adjustments can be included in all p'kinetic measurements and calculation. If the Pre-Dose value is greater than 5 percent of Cmax, the subjects should be dropped from all BE study evaluations.	Not Specified
Fluid (water) intake at Dosing	Standard quantity (one glass = 200 ml)	8 ounces(240 ml)	At least 150 ml
Position after ingestion	After dosing, volunteer should rest in supine position for standard period	Not Specified	Need to be standardized

PARAMETER	CDSCO	FDA	EMEA
Plasma storage	Stability of the drug and/or active metabolite in the biological matrix under the conditions of the experiment (including any period for which samples are stored before analysis should be established.	Not Specified	Not Specified
Wash-out period	Not less than 5 times of elimination half life..	More than 5 half lives of the moieties to be measured.	For Steady State; at least 3 times the terminal half life.
Statistical evaluation	AUC_{0-t}, $AUC_{0-\infty}$, Cmax, Tmax SS:$AUC_{0-\tau}$, Cmax, Cmin, deg. of fluctuation	AUC_{0-t}, $AUC_{0-\infty}$, Cmax, Tmax, $t_{1/2}$	AUCt, AUCinf, t_{max}, Aet, Ae_{inf}, $t_{1/2}$, MRT **SS**: AUCt, Cmax, Cmin.
Acceptance criteria for AUC ratio, Cmax etc.	90% confidence interval between 80-125%	90% confidence interval between 80-125%	90% confidence interval between 80-125%. 75-133% in certain cases.
Acceptance criteria for AUC ratio, Cmax for Narrow therapeutic range drugs.	Not Specified although mentioned that tighter limits are required.	It recommends additional tests and/or controls to ensure the quality of drug products containing Narrow Therapeutic Range Drugs. 90% confidence interval between 80-125%.	Limit is 90-110%.
Limitation for Blood Withdrawal Quantity	Care should be taken not to withdraw more than 250 ml of blood per subject in one month.	Not Specified	Not Specified
Base line collection	Not Specified	Not Specified	Not Specified
Measurement of metabolite	When parent drug not measurable, drug undergoes significant active pre systemic metabolism.	When parent drug not measurable, drug undergoes significant active pre systemic metabolism.	When parent drug not measurable, non linear PK, forms active metabolite.

PARAMETER	CDSCO	FDA	EMEA
Data deletion due to vomiting	Not Specified	**Immediate Release:** Data deletion if vomiting occurs at or before 2 times median Tmax. **Modified Release**: Data deleted any time if the subject experiences emesis during the labeled dosing interval.	Not Specified
Difference in the drug proportion between Test and Reference	Not Specified	The drug content of the test product should not differ from that of the reference listed product by >5%	Not Specified
Period for retention of drugs	3 years after conduct of study or 1 yr after expiry of drug which ever is earlier	5 years after study completion	Not specified
Quantity of drugs to be retained	Not Specified	To repeat 5 times all the release tests.	Not Specified
Period for retention of documents	Maintained by the sponsor for at least 2 years after expiration of batch.	Period of 5 years following the date on which application approved (5 yrs of completion of BE study). For at least 2 years after expiration of batch.	Not Specified

Table 2: Comparison of the regulatory requirement for the conduct of the bioavailability and bioequivalence studies mentioned in guidelines of WHO, Canada and Brazil

PARAMETER	WHO	CANADA	ANVISA
Name of the Organization	World Health organization	Health Products and Food Branch, Ministry of Health, Canada	Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency Brazil)
Country Representing	Not Applicable	Canada	Brazil
Guideline	WHO expert committee On specifications for Pharmaceutical preparations [6]	GUIDANCE FOR INDUSTRY • Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations Used for Systemic Effects,1992 [7] • Report on Bioavailability of Oral Dosage Formulations, not in Modified Release Form, of Drugs Used for Systemic Effects, Having Complicated or Variable Pharmacokinetics [8] • Bioequivalence Requirements: Comparative Bioavailability Studies Conducted in the Fed State [9]	• Guide for relative bioavailability/bioequivalence tests of drug products (May,2003) [10] • Manual for good Bioavailability and Bioequivalence Studies [11]

PARAMETER	WHO	CANADA	ANVISA
Study Design **1.General**	Two-period, single-dose, cross-over, randomized study	2 period single dose cross over fasted/fed	Open, randomized, crossover. Parallel design when necessary
2.Long half life drugs	Single-dose cross over / Parallel study	Balanced incomplete block design	Collection period of up to 72 hrs allowing determination of area under fragmented curve or parallel study
3.Highly variable drugs	Multiple-dose, steady-state, cross-over Study in patients or a parallel group design.	A cross-over design should be used. Where this is not appropriate, a parallel study will be required.	For CV> 30% replicate design.
Sample Size	minimum of 12 subjects	Not less than 12	Not less than 12. 24 in case of non availability of inter subject variation.
Replacement of subjects on withdrawal or dropout	Sponsors should select a sufficient number of study subjects to allow for possible drop-outs or withdrawals. Because replacement of subjects during the study could complicate the statistical model and analysis, drop-outs generally should not be replaced.	Two basic methods are used to account for drop-outs and withdrawals, 1. Fixed number (one or two for each sequence) of subjects are added to the sample-size number. 2. Fixed number of subjects are added into the study. These subjects are designated as extras.	Not specified
Gender of the Subject	Male/Female	Male/Female	Male/female

PARAMETER	WHO	CANADA	ANVISA
Female Subjects	The risk to women will need to be considered on an individual basis, and if necessary, they should be warned of any possible dangers to the fetus if they should become pregnant. The investigators should ensure that female volunteers are not pregnant or likely to become pregnant during the study. Confirmation should be obtained by urine tests just before administration of the first and last doses of the product under study.	The investigators should ensure that female volunteers are not pregnant or likely to become Pregnant during the study. Confirmation should be obtained by urine tests just before the first and last doses of the study.	Not specified
Age criteria	18-55 yrs	18-55yrs	18-50yrs
BMI	within the normal range	Within 15% of normal range	Within 15% of normal range
History of Smoking Criteria for Selection of Subjects	Preferably be non-smokers	It is preferable to use non-smokers; where Smokers are included, they must be so identified.	Smokers must be avoided. In case they are included, these subjects must be identified.
Restrictions (Smoking/Alcohol and Drug Abuse)	Standardization should cover the restriction of the intake of alcohol, caffeine, certain fruit juices and concomitant medicines for a specified time period before and during the study.	Volunteers should not take any other drug, including alcoholic beverages and over-the-counter (OTC) drugs, for an appropriate interval before- as well as during-the study.	Not specified

PARAMETER	WHO	CANADA	ANVISA
History of Alcohol and Drug Abuse Criteria for Selection of Subjects	Subjects should have no history of alcohol or drug abuse problems.	Not Specified	Subjects with a H/O of alcohol and drug abuse must be avoided.
Food Specification for Fed Studies	A high-fat meal often provides a maximal challenge to the robustness of release from the formulation with respect to prandial state. The composition of the meal should take local diet and custom into consideration.	An example of a test meal that is expected to promote the greatest perturbation in gastrointestinal physiology so that systemic drug BA is maximally affected would be the following breakfast: 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter,120 gm of hash browns and 240 ml of whole milk. Sponsors must be able to justify the choice of meal in a fed BE study and relate the specific components and timing of food administration.	Not Specified
No. of Samples	Sampling points should include a pre-dose sample, at least 1–2 points before Cmax, 2 points around Cmax and 3–4 points during the elimination phase. It is currently not foreseen that there would be a need for blood samples to be collected for more than 72 hours.	12-18 samples per subject per dose, duration of at least 3 terminal half lives.	Equal or greater than 3-5 times the half-life of elimination of the drug or the metabolite.

PARAMETER	WHO	CANADA	ANVISA
Water Restriction	On the morning of the study no water is allowed during the hour prior to drug administration. Two hours after drug administration water is again permitted ad libitum.	On the morning of the study, up to 250 mL of water may be permitted up to two hours before drug administration. Two hours after Drug administration, 250 mL of xanthine-free fluids are permitted.	Not Specified
Fasting prior to study	Overnight fast of at least 10 hours.	Fasting 10hrs before Dosing A fast means that no food or solids are to be consumed, although alcohol-free and xanthine-free clear fluids are permissible the night prior to the study.	8 hrs before and 4 hrs after dosing.
Subjects with Pre-dose plasma conc.	Not Specified	Not Specified	Not Specified
Fluid (water) intake at Dosing	Standard volume of water (usually 150–250 ml).	At least 150 ml at a standard temperature.	Must be standard usually 200 ml.
Position after ingestion	Physical activity and posture should be standardized as far as possible to limit their effects on gastrointestinal blood flow and motility. The same pattern of posture and activity should be maintained for each day of the study.	Recline until at least 2 hrs after ingestion of drug.	Not specified

PARAMETER	WHO	CANADA	ANVISA
Wash-out period	Five times the terminal half-life of the API. The minimum wash-out period should be at least seven days. The adequacy of the wash-out period can be estimated from the pre-dose Concentration of the API and should be less than 5% of Cmax .	Not less than 10 times of mean terminal half life	Minimum 7 half lives
Plasma storage	Not Specified	Appropriate storage conditions should be confirmed with samples.	Standardized and in cases where it is necessary to transport the biological samples (plasma, serum or urine) the procedure for good laboratory practice must be followed in order to preserve the characteristics of the material to be analyzed. Use appropriate packing (certified) for preservation and transport. The temperature of the biological sample must be recorded with calibrated device to ensure maintenance of stability during the period of transport.

PARAMETER	WHO	CANADA	ANVISA
Statistical evaluation	AUC0→t, AUC0→∞, Cmax, Tmax, t1/2	AUC_{0-t}, $AUC_{0-\infty}$, Cmax, Tmax, $t_{1/2}$	AUC_{0-t}, Cmax, Tmax, $t_{1/2}$
Acceptance criteria for AUC ratio, Cmax etc.	90% confidence interval between 80-125%	90% confidence interval between 80-125%	Between 80-125% [10]
Acceptance criteria for AUC ratio, Cmax for Narrow therapeutic range drugs.	Acceptance range may need to be reduced based on clinical justification.	Not Specified	Not Specified
Limitation for Blood Withdrawal Quantity	Not Specified	Not Specified	Not Specified
Base line collection	Not Specified	Not Specified	Not Specified

CONCLUSION

The widely used regulatory guidelines in India were identified which mentions the regulatory requirement for the conduct of bioavailability and bioequivalence studies by the respective regulatory authorities. This comparison involves comparing six widely used regulatory guidelines such as FDA (Food and Drug Administration, USA), EMEA (European Agency for the evaluation of Medicinal Products, Europe), ANVISA (National Health Surveillance Agency Brazil), CDSCO (Central Drugs Standard Control Organization, India), WHO (World health Organization) and presenting them in a common platform which enables uncomplicated understanding. The regulatory guidelines were compared on the basis of various parameters involving the clinical conduct of the bioavailability and bioequivalence studies.

The comparison made is of benefit to fraternity in Clinical Research Organization and Pharmaceutical Industry as it aids them in understanding the conduct of such studies mentioned in the guidelines in a common platform, this will aid them in conducting the studies according to the requirements of the respective guidelines for the country they filling the ANDA. The comparison is also of benefit to the academic fraternity as it will open a new arena for understanding the regulatory aspects of the conduct

of the bioavailability and bioequivalence studies. This opens a window in the common platform of clinical as well as regulatory aspects of bioavailability and bioequivalence studies.

With recent reports of the study subjects being used as guinea pigs in clinical research, this comparison throws light on the ethical conduct of such studies which is of interest to academicians, clinical researchers and the Pharmaceutical companies and it can be said that for India to continue as a global hub of bioavailability and bioequivalence studies, it is of paramount importance that the studies are conducted in par with the requirements of the regulatory authorities. This comparison throws light on this aspect of clinical research.

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