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An Overview on Bioequivalence: Regulatory Consideration for Generic Drug Products

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Abstract

Generic pharmaceutical products need to confirm to the same standards of quality, efficacy and safety as required of the originator's (innovator) product. Specifically, the Generic product should be therapeutically equivalent and interchangeable with the reference product. Testing the bioequivalence between a test product pharmaceutically equivalent or a pharmaceutical alternative and a suitable reference product in a pharmacokinetic study with a limited number of subjects is one way of demonstrating therapeutic equivalence. Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical and clinical data to establish safety and effectiveness. This paper provides the information about important aspect involved in bioequivalence and Regulatory requirement for Bioequivalence study.

Keywords: US FDA; EMEA; MCC;Body mass index;Confidence interval; AUC

Abbreviations: FDA: Food and Drug Administration; EMA: European medical agency; BA/BE: Bioavailability and Bioequivalence; MCC: Medicine control council; AUC: Area under Curve; ANDA: Abbreviated new drug application

Introduction

Generic drug

According to the U.S. Food and Drug Administration (FDA), generic drugs are identical or within an acceptable bioequivalent range to the brand name counterpart with respect to pharmacokinetic and pharmacodynamic properties. By extension, therefore, generics are considered (by the FDA) identical in dose, strength, route of administration, safety, efficacy, and intended use. The FDA's use of the word identical is very much a legal interpretation, and is not literal. In most cases, generic products are available once the patent protections afforded to the original developer have expired. When generic products become available, the market competition often leads to substantially lower prices for both the original brand name product and the generic forms.

Hatch waxman act

Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Waxman-Hatch Act. Under Hatch-Waxman Act, one of the following four certifications has to be made while filing an ANDA: [Food and drug administration, center for drug evaluation and research (CDER)].

Type	Patent Certification	ANDA Filing
Paragraph I	The drug has not been patented.	If a generic drug manufacturer certifies I & II, then the FDA starts processing the generic ANDA right away
Paragraph II	The patent has already expired.	
Paragraph III	The generic drug will not go on the market until the day of expiry of the patent	If a generic drug manufacturer certifies 3, then the FDA starts processing the ANDA, and gives approval when the patent expires
Paragraph IV	The patent is not infringed or is invalid	ANDA filer notifies patent holder within 20 days – Patent holder must sue for infringement within 45 days – If the patent holder sues, FDA must withhold approval for 30 months (one time only) – If the patent holder does not sue, FDA may approve ANDA at any time – If a court rules that the patent is not infringed or invalid, FDA may proceed after decision. – If first generic ANDA files will gets 180 days exclusivity (per product)

Important aspect involved in bioequivalence and Regulatory requirement

a) Standardisation of study: The test conditions should be standardised in order to minimise the variability of all factors involved except that of the products being tested. Bioequivalence study will be carried out in healthy volunteer unless drug carried safety issue it will carry out in patient(US FDA General consideration BA/BE, 2003).

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i) Demographic requirement:

Regulatory Agency	Age (year)	BMI (kg/m^2)	SEX
U.S.A	18 years of age or older	18.5 - 24.9	Both sex
Europe	18 years of age or older	18.5 - 30	Both sex
Japan	Healthy adult volunteers	18.5-25.0	--------
Canada	18 to 55 older	Height/weight ratio for healthy volunteer subjects should be within 15 percent of the normal range.	Both sex
Australia	Between 18-55	Accepted Normal BMI	Both sex
Saudi Arabia	Between 18-50	Within 15% of ideal body weight, height and body build.	If females are included in the study, the effects of gender differences and menstrual cycle (if applicable) are examined statistically.
ASEAN	Between 18-55	18.5 and 25 kg/m^2	Both sex
South Korea	19-55	---	----
Mexico	18 and 55	weight 10% from the ideal weight	To avoid pharmacokinetic differences between sexes is well documented; volunteers of just one sex must be included.
China	18 to 40 years of age generally, the same subjects were not different from 10 years of age.	Standard weight range.	Both sex

ii) Diet and fluid requirement:

Regulatory Agency	Diet	Fluid intake
Europe and Australia	i) No food is allowed for at least 4 hours post-dose. Meals taken after dosing should be standardised in regard to composition and time of Administration during an adequate period of time**. (fasting study)** ii) In fed conditions, the timing of administration of the drug product in relation to food intake is recommended to be according to the SmPC of the originator product. If no specific recommendation is given in the originator SmPC, it is recommended that subjects should start the meal 30 minutes prior to administration of the drug product and eat this meal Within 30 minutes**. (fed study)** (Europe BA/B CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *)	i) Test and reference products should be administered with a standardised volume of fluid (at least 150 ml). ii) Water is allowed as desired except for one hour before and one hour after drug administration
Japan	-similar to U.S.A. -If bioavailability under fasting conditions is markedly low, or a high incidence of severe adverse effects is indicated, drugs may be given postprandial. For a postprandial dose, the meal should be eaten within 15 minutes, and the drug administered according to the dosing regimen or 30 minutes.(NIHS Japan, 2000)	-Similar to Europe
Canada	- Similar to Europe -All meals should be standardized and repeated on each study day. (HPB BA/BE, 2009)	- Similar to Europe - When comparing the performance of two orally disintegrating dosage forms that are intended to be taken without water, the comparative bioavailability study should be designed to challenge the formulation under the most discriminatory conditions. For such dosage formulations, water should not be administered from one hour prior to dosing, concurrent with dosing and up to one hour post dosing.
U.S.A.	- No food should be allowed for at least 4 hours post-dose -Subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. - Standardized meals scheduled at the same time in each period of the study (US FDA BA/BE, 2003)	i) Subjects should be administered the drug product with 240 mL (8 fluid ounces) of water. ii) Water is allowed as desired except for one hour before and one hour after drug administration
Saudi Arabia	-Similar to Europe - Standard meals for each study periods can be provided no less than 4 hours after drug administration	-The drug product should be administered with 180 ml of water immediately - Water can be allowed ad libitum after 2 hours.
ASEAN	-As per Saudi Arabia	-As per Europe -Hot drink or juice may be provided after 3 hours of drug administration
South Korea	Similar to U. S.	Similar to U. S.

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Mexico	Volunteers' diet during the study should be homogeneous and consistent with its own design(Guidance for medication interchangeability, 1999).	Medications must be administered via oral route with 250 mL of water. In the case of requiring a different volume, it must be scientifically justified and be homogeneous for medications with the same drug. (Guidance for medication interchangeability, 1999).
Japan special requirement -Subjects with low gastric acidity are required in cases where the average dissolution percent of a slower dissolution product is less than 50% at the time when the average dissolution of a faster dissolution product reaches 80% in water or neutral test solution. However, this rule is not applied to rapidly dissolving products when more than 85% of the drug dissolves from both products in water or neutral test solution. -For basic drugs for which dissolution tests cannot be conducted using water or neutral solution because of low solubility, selection of subjects should be based on the results obtained at around pH 3-5. -If clearance of drugs largely differs among subjects due to genetic polymorphism, it is recommended that subjects with higher clearance be employed. -If the use of drugs is limited to a special population, and dissolution profiles differ significantly between reference and test products, bioequivalence studies with subjects of the population may be needed.		

iii) Fasting requirement:

Regulatory Agency	Fasting
Europe	At least 8 hours prior to administration of the products and no food is allowed for at least 4 hours post-dose.
Japan	At least 10 hours of fasting which is continued for at least 4 hours post-dose.
Canada	
Saudi Arabia	
South Korea	
U.S.A	
ASEAN and Australia	At least 8 hours prior to administration of the products. If the Summary of Product Characteristics of the reference product contains specific recommendations in relation with food intake related to food interaction effects the study should be designed accordingly
Mexico	volunteers must be fasting for at least 10 hours before administering the medication and for at least two hours after administration

b) Fed study Requirement: As per US, Europe, TGA a high fat and a high caloric meal are recommended as test meal for Fed BE study. Fat should be 50 % of total caloric content of the meal and 800 to 1000 calories considered as high calories. As per US, Europe, TGA regulation meal should contain 150 calories of protein, 250 calories of carbohydrates and 500-600 calories of fat. But In NIHS (Japanese, 2000) guidance the low fat and high caloric food is recommended. The caloric content is approximately 700 kcal out of which not more than 20% (140 kcal) is derived from the fat.

c) Sample size: Number of subject will be selected depend up on the variability of drug and acceptance criteria of drug. The minimum number of subject for crossover design will be 12 but appropriate sample size will be determined based on previous available data or data available from pilot study. (BE Guideline of Saudi Arabia, 2005).

Regulatory Agency	Minimum	Maximum
U.S.A and South Korea	12	The total number of subject in the study should provide adequate power for BE demonstration.
Europe	12	-Not Specified in BE Guideline -ICH E9 section 3.5 applies which state ' The number of subject in clinical trial should always large enough to provide a reliable answer to the question addressed
WHO	12	
Canada	12	
Australia	12	
ASEAN	12	-Not Specified in BE Guideline
Malaysia	12	
Argentina	12	
Japan	20	
Brazil	24	
Saudi Arabia	12-24 (I statistically justifiable)	
New Zealand	12	If the calculated number of subject to be higher than is ethically justifiable, it may be necessary to accept a statistical power which is less than desirable. Normally it is not practical to use more than about 40 subject in bioavailability study
Mexico	Sample size must not be smaller than 24 subjects considering both sequences or it must meet the requirement related to a difference to be detected of ± 20% regarding the reference product's mean, associated with a type-I error (*) of 0.05 and a minimal potency of (1-*) of 0.8 for this kind of design. A sample size smaller than 24 subjects must be scientifically justified. (Mexican Official journal of Medication interchangeability (1999) section I: 50).	Not Specified in BE Guideline

Dropout and withdrawn

As per U.S. Saudi Arabia, Asian, Mexico, South Africa regulatory recommend that Sponsors should enroll a sufficient number of subjects in the study with consideration for dropouts and withdrawn from study due to related adverse event or any other reasons. Because replacement of subjects could complicate the statistical model and analysis, dropouts generally should not be replaced.

Add on design

There might be chance that study sample size calculation does not give accepted result. Following countries provided Add on approach for such study along with there application.

Regulatory Agency	Add on
Europe & Australia	It is acceptable to use a two-stage approach when attempting to demonstrate bioequivalence. An initial group of subjects can be treated and their data analysed. If bioequivalence has not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis. If this approach is adopted appropriate steps must be taken to preserve the overall type I error of the experiment and the stopping criteria should be clearly defined prior to the study. The analysis of the first stage data should be treated as an interim analysis and both analyses conducted at adjusted significance levels. (Europe BA/BE CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *).
Japan	Also for add on study additional 10 subjects are recommended along with initial subjects
Canada	As a result of random variation or a larger than expected relative difference, there is no guarantee that the sample size as calculated will pass the standards. If the study is run with the appropriate size and the standards are not met, the sponsor may add more subjects (a minimum of 12). The same protocol should be used (i.e., same formulations, same lots, same blood sampling times, a minimum number of 12 subjects, etc.). The choice to use this strategy, as with all designs, should be declared and justified a priori. The level of confidence should be adjusted using the Bonferroni procedure. The t-value should be that for p=.025 instead of .05. (HPB BA/BE Canada, 2009)
South Africa	If the bioequivalence study was performed with the appropriate size but bioequivalence cannot be demonstrated because of a result of a larger than expected random variation or a relative difference, an add-on subject study can be performed using not less than half the number of subjects in the initial study. Combining is acceptable only in the case when the same protocol was used and preparations from the same batches were used. Add-on designs must be carried out strictly according to the study protocol and SOPs, and must be given appropriate statistical treatment, including consideration of consumer risk.(MCC Guideline version 3 Jun 2010).

d) Type of study: The number of studies and study design depend on the physico-chemical characteristics of the substance, its pharmacokinetic properties and proportionality in composition, and should be justified accordingly. Various regulatory provide detail regarding type of study required to be carried out shown below.

Regulatory Agency	Immediate Release	Modified Release
U.S.A	**Total of 2 studies**: 1 single dose crossover study fasted 1 single dose crossover study, fed* * If food mentioned in the product Monograph if a multiple-dose study design is important, appropriate dosage administration and sampling be carried out to document attainment of steady state.	**Fasting and fed** If a multiple-dose study design is important, appropriate dosage administration and sampling be carried out to document attainment of steady state.
Europe & Australia	**Total of 1-2 studies:** 1 single dose crossover study, Fasted. **OR** Fed condition according to SmPC Recommendations related with food interaction effects. (Europe BA/BE CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *).	Fasting, fed and steady state
Japan	Fasting and fed	Fasting, fed and steady state
Canada	Fasting	Fasting and fed If Steady-state studies are required, the food and fluid conditions and restrictions noted above should apply on the preceding evening and on the day the plasma profiles are to be obtained. .(HPB BA/BE Canada, 2009).
Saudi Arabia	Fasting and if food effect from document evidence or drug requires to be administered in fed condition in this case fed study required.	Fasting and fed
South Korea	Fasting	Fasting fed and steady state

e) Strength to be investigated: 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. The strength(s) to evaluate depends on the pharmacokinetics of the active substance.

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Regulatory Agency	Linear Pharmacokinetics	Non Linear Pharmacokinetics
U.S.A	Reference Listed Drug (RLD) in the Orange Book* *usually the highest strength if formulations are proportionally similar	Not addressed in Guidances. Refer to Reference Listed Drug (RLD) in the Orange Book
Europe & Australia	The bioequivalence study should in general be conducted at the highest strength Highly soluble drug and any safety concern: Lower strength acceptable Problems of sensitivity of the analytical method: Highest strength acceptable	* For drugs with non-linear pharmacokinetics characterized by a more than proportional increase in AUC with increasing dose over the therapeutic dose range, the bioequivalence study should in general be conducted at the highest strength. As for drugs with linear pharmacokinetics a lower strength may be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. Likewise a higher dose may be used in case of sensitivity problems of the analytical method in line with the recommendations given for products with linear pharmacokinetics above. * For drugs with a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established both at the highest strength and at the lowest strength (or strength in the linear range), i.e. in this situation two bioequivalence studies are needed. If the non-linearity is not caused by limited solubility but is due to e.g. saturation of uptake transporters and provided that a) same manufacturing process b) Qualitative composition of the different strengths is the same c) composition of the strengths are quantitatively proportional d) appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo Bioequivalence testing and the test and reference products do not contain any excipients that may affect gastrointestinal motility or transport Protein, it is sufficient to demonstrate bioequivalence sport proteins at the lowest strength (or strength in the linear range). (Europe BA/BE CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *).
Canada	Use strength with largest sensitivity to identify differences in formulation	
Saudi Arabia	For conventional (immediate release) solid oral drug products, in vivo bioequivalence studies are conducted on the highest strength. This requirement for the lower strengths can be waived provided: (a) in vivo bioequivalence is demonstrated on the highest strengths; (b) in-vitro dissolution testing is acceptable; and (c) the formulation for the lower strengths are proportionally similar to the strength which has undergone in vivo bioequivalence testing (i.e., the ratio of active ingredients and excipients between the strengths is essentially the same).	Not addressed in Guidances

f) Parameter to be determined: For single dose study pharmacokinetic parameter C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ residual area T_{max}, Kel, $t_{1/2}$ is determined using plasma time concentration profile of drug For multiple dose studies $AUC_{(0-\tau)}$, $C_{max,ss}$ and $t_{max,ss}$ determined using plasma time concentration profile of drug. (FDA BA/BE General consideration 2003).

g) Statistical analysis: Statistical analysis will be performed on the data obtained from subjects. Descriptive statistics of all the pharmacokinetic parameters will be computed and reported. (FDA BA/BE Statistical approach 2001; Rani and Pargal, 2004).

Analysis of variance (ANOVA): The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of analyte will be subjected to Analysis of Variance (ANOVA). ANOVA model will include Sequence, Formulation and Period as fixed effects and Subject (Sequence) as a random effect. Sequence effect will be tested using Subject (Sequence) as error term. The significance of the sequence effect at alpha 0.10 will be tested using the subjects nested within the sequence as the error term. An F-test will be performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha =0.05).

Power: The power of a test to detect 20% difference between test and reference formulations will be computed and reported.

Ratio analysis: Ratio of least squares means of test and reference formulations will be computed for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.

Ratio analysis will be reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for analyte.

Intra-subject variability: Intra-Subject variability will be computed for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for analyte.

Acceptance parameter for bioequivalence: Two one-sided test for bioequivalence and 90% confidence intervals for the ratio of least squares mean between drug formulations will be calculated, for ln-transformed data of $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ for single dose study and $AUC_{(0-\tau)}$ and $C_{max,ss}$ for multiple dose study.

In Europe and South Korea guideline suggest that if the drug having long half life and sampling duration is more than 72 hours. In this case AUC is truncated upto 72 hr and no need to measures $AUC_{0-\infty}$ and residual area.

h) Acceptance criteria for bioequivalence:

Regulatory Agency	90 % confidence interval on Log transformed data		
	C_{max} %	AUC_{0-t} %	$AUC_{0-\infty}$ %
U.S A.	80-125	80-125	80-125
Europe & Australia	80-125	80-125	Not Applicable
Canada	Ratio must be between 80-125 Need to pass also on potency corrected data. Add-on studies may be allowed if intra- CV greater than expected	80-125	Not Applicable
South Africa	75-133	80-125	Not Applicable
Saudi Arabia	80-125	80-125	80-125
ASEAN	80-125	80-125	80-125
South Korea	80-125	80-125	80-125
Mexico	80-125	80-125	Not Applicable

Japan:
Products are considered to be bioequivalent, if the 90% confidence interval of difference in the average values of logarithmic AUC and Cmax between test and reference products is within the acceptable range of log(0.8) - log(1.25). However, even though the confidence interval is not in the above range, test products are accepted as bioequivalent, if the following three conditions are satisfied (NIHS Japan, 2000).
1) The total sample size of the initial bioequivalence study is not less than 20 (n=10/group) or pooled sample size of the initial and add-on subject studies is not less than 30,
2) The differences in average values of logarithmic AUC and C_{max} between two products are between log (0.9) - log (1.11)
3) Dissolution rates of test and reference products are evaluated to be equivalent as per dissolution test. The dissolution characteristics of the test product must be similar to those of the reference product under all of the following conditions when dissolution tests are performed according to the dissolution tests for oral conventional dosage forms and enteric coated products. Either the rotating basket or disintegration testing apparatus can be selected, the reason for which should be stated. The testing times are 2hr in pH 1.2 medium and 24 hr in other test fluids. The test can be ended at the time when the average dissolution of reference product reaches 85%. However, the 3rd rule can not be applied to slowly dissolving products from which more than 80% of a drug does not dissolve within the final testing time (2hr in pH 1.2 medium and 6 hr in others) under any conditions of the dissolution tests described in Sec.3 A.V. of Japan guideline.

South Korea:
If the values are not between log 0.8−log 1.25, then the test drug product is considered BE, if all the following are met: (Korea FDA Notification #2008–22 May 07, 2008)
1. In case the difference between the log-transformed mean values of comparative parameters of the test and reference drug products is within log 0.9−log 1.11;
2. In case the results of the dissolution test between the test and reference drug products are equivalent under all test conditions, according to the Regulation for the Management of the therapeutic Equivalence Test (KFDA Notification), although this provision is not applicable to solid oral preparations (except for controlled-release preparations) and enteric coated preparations, unless the average dissolution rate from the reference drug product reaches 85% within the specified time point (For controlled-release preparations, the average dissolution rate from the test drug product reaches within ± 10% of the average dissolution from the reference drug product at the time point at which the reference drug product dissolves at around 30, 50, and 80%); and
3. The total number of subjects should be more than 24 (12 per group).

Acceptance Criteria for bioequivalence for special class drug:

Regulatory Agency	Narrow therapeutic index drugs 90 % confidence interval Log transformed data		Highly variable drugs 90 % confidence interval Log transformed data	
	C_{max},	AUC_{0-t}	C_{max}	AUC
U.S.A	**80-125**	**80-125**	GMR (80 -125) 95% upper bound for (μT - μR) / ϭ2WR ≤ 0.7976 (Using Scaled Average Approach)	GMR (80 -125) 95% upper bound for (μT - μR) / ϭ2WR ≤ 0.7976 (Using Scaled Average Approach)
Europe	90.00-111.11	90.00-111.11	-----	
Japan				
Canada			GMR (80 -125)	GMR (80 - 125) 90% CI (80 – 125)
Saudi Arabia	90-111	-----	75-133	wider acceptance range may be acceptable and this should be justified clinically
ASEAN	acceptance interval may need to be tightened	acceptance interval may need to be tightened	The interval must be prospectively defined e.g. 0.75-1.33 and justified addressing in particular any safety or efficacy concerns for patients switched between formulation	In rare cases a wider acceptance range may be acceptable if it is based on sound clinical

Europe guideline for highly variable drug: Highly variable drug products (HVDP) are those whose intra-subject variability for a parameter is larger than 30% (Europe BA/BE CPMP/EWP/QWP/1401/98 Rev. 1/ Corr *). If an applicant suspects that a drug product can be considered as highly variable in its rate and/or extent of absorption, a replicate cross-over design study can be carried out. Those HVDP for which a wider difference in C_{max} is considered clinically irrelevant based on a sound clinical justification can be assessed with a widened acceptance range. If this is the case the acceptance criteria for C_{max} can be widened to a maximum of 69.84 – 143.19%. For the acceptance interval to be widened the bioequivalence study must be of a replicate design where it has been demonstrated that the within-subject variability for Cmax of the reference

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compound in the study is >30%. The applicant should justify that the calculated intra-subject variability is a reliable estimate and that it is not the result of outliers. The request for widened interval must be prospectively specified in the protocol.

The extent of the widening is defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence according to [U, L] = exp [±k·sWR], where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and sWR is the within-subject standard deviation of the log-transformed values of Cmax of the reference product. The table below gives examples of how different levels of variability lead to different acceptance limits using this methodology.

Within-subject CV (%)*	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

The geometric mean ratio (GMR) should lie within the conventional acceptance range 80.00-125.00%. The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC where the acceptance range should remain at 80.00 – 125.00% regardless of variability. It is acceptable to apply either a 3-period or a 4-period crossover scheme in the replicate design study.

Conclusion

Today, various pharmaceutical companies developing generic drug products. Bioequivalence study is important for generic drug approval process. It is our hope that, this review will provide 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.

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