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Review Article

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Bioequivalence requirements of Pharmaceutical Products in US, Europe and Australia

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Abstract

In the last three decades, the notion of bioequivalence has gotten a lot of attention as it has been applied to new branded and generic medications. Generic medications must meet the same quality, efficacy, and safety requirements. Conventional products should be therapeutically equal to the reference product and compatible. The evolution of regulatory standards for bioequivalence in the United States, Europe, and Australia are examined in this paper. There is no international harmonization of regulatory requirements for bioequivalence, but the scope of bioequivalence and statistical analysis is partially harmonized; however, there are differences in applying single-dose trials and in vitro dissolution tests due to subject selection and reference product selection. The drug management system and drug regulating laws determine the pharmaceutical market's share. A bioequivalence study is one of the essential elements in the generic medicine approval process. The plasma time-concentration curve is frequently used in bioequivalence studies to determine absorption pace and absorption. The bioequivalence of the goods examined can be determined using the selected pharmacokinetic parameters and predefined acceptability thresholds. Recent advancements and information on crucial areas of bioequivalence study design and specification recommendations for each endpoint are included in this review

Keywords: Bioequivalence, Bioavailability, Pharmacokinetics, Fasting and Fed Studies, ICH GCP, biowaiver, Biopharmaceutics Classification System (BCS), USFDA, EMA, TGA.

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1. Introduction

A regulatory body's job is to ensure consistency in quality, efficacy, and safety standards for pharmaceutical products. The study focuses on the evolution of bioequivalence regulatory standards in the USFDA (United States Food and Drug Administration), EMA (European Medicines Agency), and TGA (Therapeutic good Administration). A bioequivalence study is required before a generic drug product may be submitted to a regulatory agency. The term "bioequivalence study" refers to a human clinical study that uses BA Study methods and pK parameters as indicators to compare active moiety absorption rate and extent of preparation in the same or different dosage forms of the drug in terms of statistical differences under the same experimental conditions. BE studies are used to complete New Drug Applications, Generic Drug Applications, and Hybrid Applications. BE Study is established using pharmacokinetics [how the body reacts to the medicine], pharmacodynamics, clinical trials, and in-vitro studies. Clinical and in-vitro research is the most precise, sensitive, and repeatable BE method. BE study is a legal requirement in the United States, Europe, and Australia for filling generic medications. Benefits of BE study: 1) Allows interchangeability/substitution of one product by another equally effective product. 2) Minimize variations of efficiency and safety of the product from batch to batch produced by the same company.3) Helps introduce generic drugs of innovator drugs at a lower cost. 4) Helps in improving the formulation by reducing the formulation variables. (1)

2. General approaches to establishing bio-equivalence

- ***Concern department & workflow for bioequivalence.***

As shown in the above figure, there are Three Concern departments established for BE study:1) Clinical/Protocol team, 2) Bioanalytical Department, 3) Statistical/Report department. (2, 3)

- ***Fasting and Fed Studies***

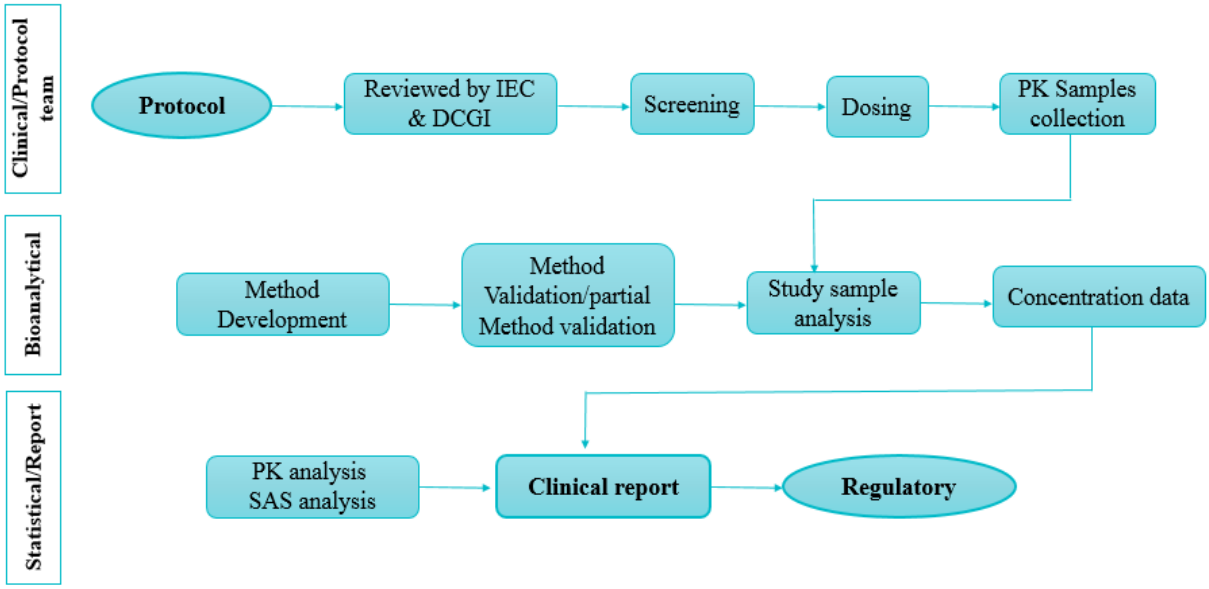

Figure 1. Flow of Concern Department

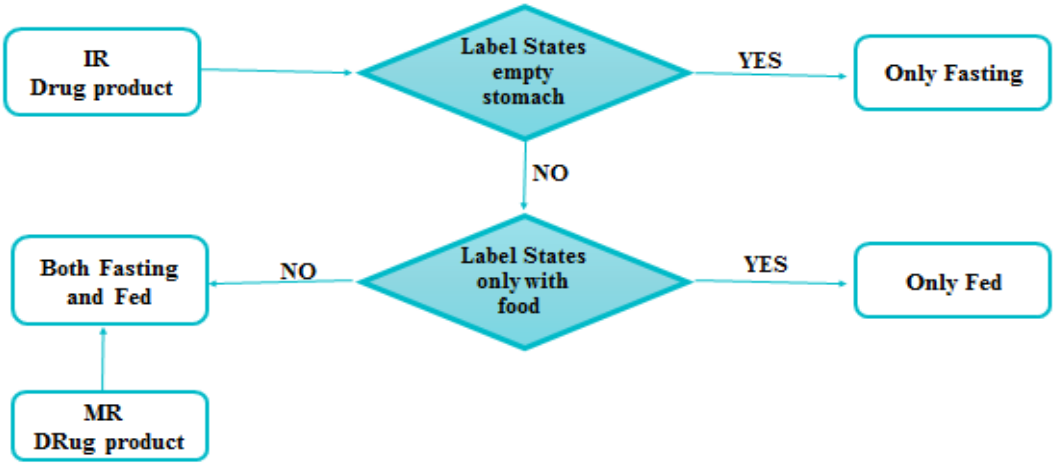

Figure 2. Fasting and Fed Studies

As shown above, For the immediate release dosage form, if the label states empty stomach, perform a fasting study, and if the label states only with food, then perform Fed Study. If the label does not recommend it, perform Fasting Study and Fed Study. For Modified Release dosage form, perform both study Fasting and Fed. (2-4)

- ***Alternative approaches***

If it is impossible to measure PK parameters, pharmacodynamics (PD) approaches can be employed to demonstrate bioequivalence, although PK investigations are recommended. Finally, comparative clinical trials may be considered if all other options fail. Nonetheless, this is the least desirable alternative, both from the sector's standpoint and from the perspective of the authority, due to the lack of sensitivity for BE reasons.

- ***In vitro "bio" equivalence studies***

In vitro "bio" equivalence ponders in the case of proportionality waivers; in vitro dissolution tests can be utilized rather than in vivo BE tests. In such thinks, the restorative Product is presented into apparatus that permits for the evaluation of cumulative dissolution over time in an aqueous buffered medium at three distinctive pH levels (pH 1.2, 4.5, and 6.8) and, on the off chance that pertinent, the batch release method (quality control method). (5)

- ***Waivers***

USA and EU accepted biowaivers based on the Biopharmaceutics Classification System (BCS), and Australia follows European Guidelines. In the USA, the drug product must be BCS Class I; in the EU, both BCS Class I and III products are accepted for BCS-based Biowaiver. The BCS-based Biowaiver approach constitutes a surrogate for in vivo bioequivalence testing based on physical-chemical drug substance characteristics and comparative in vitro dissolution of test and reference.

Moreover, in the case of IR and MR formulations, it may be possible to waive in vivo studies for some strengths, replacing the in vivo studies with certain in vitro dissolution tests. In this context, the US-FDA

uses the term "waiver request," whereas the EMA uses the term "Biowaiver of strengths" (5)

- ***Bioequivalence data for submission***

BE data is required for generic product applications and submitted in the eCTD format. BE data is needed in Module-2 (Summary of common technical documents) and Module -5 (Clinical report). (6)

3. US-FDA regulatory review

In the USA, the regulation regarding BE Studies are divided into two Guidelines: post-approval changes and generics. The office of Generic Drugs within the US-FDA is responsible for all guidance relating to BE studies for generics, whereas the Scale-Up and Post Approval Changes (SUPAC) Task Force within the Centre for Drug Evaluation and Research (CDER) takes care of the recommendations for variations to approved products. Bioequivalence study required for New Drug Application (Characterization of basic pharmacokinetics, Absolute and relative bioavailability study and Food effect), Abbreviated New Drug Application (BE of test with RLD Fasting and Fed study) and Post-approval Changes (BE post-approval changes Product vs. RLD) But here only focused in generic for BE study regulation. In the USA Code of Federal Regulation, 21 CFR Part 320, "Bioavailability and bioequivalence requirements" regulations follow. In the USA, they do not give separate guidelines for immediate release dosage forms and Modified release dosage forms. (5-7)

5. EMA regulatory review

The European Medicines Agency (EMA) has given the separate guideline for immediate release dosage forms and Modified release dosage forms. Bioequivalence study required for Hybrid Application (Characterization of basic pharmacokinetics, Absolute and relative bioavailability study, and Food effect), Generic Application (BE of test with ERP Fasting and Fed study), and Post-approval Changes (BE post-approval changes Product vs. ERP) But here only focused in generic for BE study regulation. Guideline on the Investigation of bioequivalence. [Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **] of 2010 is focused on Oral Immediate release dosage forms and guidelines on the pharmacokinetic and clinical evaluation of modified release dosage forms. [Doc. Ref. EMA/CHMP/EWP/280/96 Rev1] of 2014 focuses on the modified release dosage forms. (8-10)

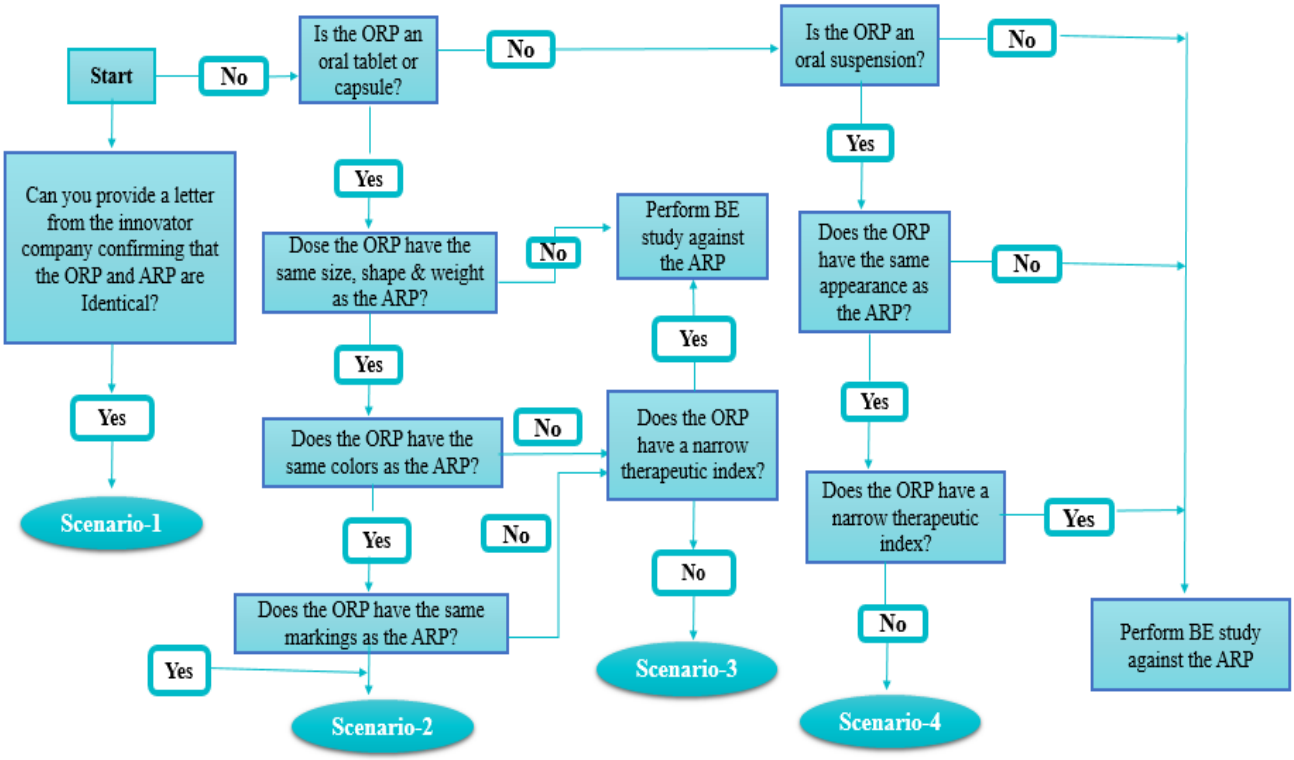

Figure 3. Australia Regulatory review

4. Australia Regulatory Review

Therapeutic Good Administration (TGA) gives guidance to Biopharmaceutic studies (version 1.2) related to applications for market authorization of medicines that require demonstration of bioavailability and bioequivalence, and generally, Australia follows the regulations and guidelines of the European Medicines Agency (EMA). Australia has four scenarios for BE studies, as depicted in the figure above. For Scenario-I, if the innovator company provides a letter confirming that ORP and ARP are identical. If the ORP is an oral tablet or capsule, they have the same size, shape, weight, color, and markings as ARP as Scenario-2. If ORP hasn't an oral tablet or capsule no same size, shape, & weight, perform BE study against the ARP. (11)

Also, they don't have the same colors, marking as the ARP, and they have no narrow therapeutic index considered Scenario-3. If ORP has a narrow therapeutic index, perform BE study against the ARP. If ORP is oral Suspension, same appearance and no therapeutic index, consider Scenario-4, if they do not

have the same appearance as ARP and have a narrow therapeutic index, perform BE Study against the ARP. (11)

Table 1. Comparison of Bioequivalence studies requirements in US, Europe, and Australia (5,7-12)

Sr. No.	BE Study Requirements	USA	Europe	Australia
1.	Regulatory Agency	The United States Food and Drug Administration	European Medicines Agency	Therapeutic Goods Administration
2.	Reference Product Type	Reference Listed Drugs [RLD],	European Reference Product [ERP].	The Australian reference product [ARP] or Overseas reference product.
3.	Reference Source	Only the US market should be used to source the reference product.	The reference product must only come from within the European Union.	The reference product needs to be sourced from Australia or a foreign market.
4.	Reference product substitute	If the reference product is no longer available, a generic product expressly identified in the orange book can be chosen as the reference product, referred to as the Reference Standard.	Not Applicable	EU/US reference standard use
5.	Subjects	At least Not less than 12 subjects.	At least Not less than 12 subjects.	At least Not less than 12 subjects.
6.	Gender	Both sexes	Either Sex/ both sexes	Either Sex/ both sexes
7.	Age Criteria	Eighteen years of age or older.	Eighteen years of age or older.	Eighteen years of age or older.
8.	Test Product	Test products are typically from at least 1/10 production scale or 100,000 units, whichever is more extensive unless specifically justified. The batch production should provide a high level of assurance that the product and process will be feasible	Test products are typically from at least 1/10 production scale or 100,000 units, whichever is more extensive unless specifically justified. If your production batch is less than 100,000 units, you need a complete production batch. The comparative dissolution profile should be run in the first three production batches.	Follow European Guideline.
9.	Body Mass Index	Not Specified / Follow limit of EU guideline	BMI between 18.5 and 60 kg/m^2	Accepted normal BMI.
10.	Fasting Study	A fast of at least 10 hours lasted at least 4 hours after administration.	Unless you have a good reason, you should not eat at least 8 hours before dosing and at least 4 hours after administration.	Follow European Guideline.
11.	Fed Study	Recommended 30 Min. before administration of the drug and 30 min after meal. or PSG	Recommended 30 Min. before administration of the drug and 30 min after meal. or SmPC	Follow European Guideline.
12.	Water/fluid intake	The drug can be administered on an empty stomach with approximately 8 ounces or 240 ml of water, and the water can be taken 1 hour in advance. And after 1 hour of drug administration.	The drug can be administered with 150 ml of water during each study, and drink water before one hr. and after one hr. drug administration.	Follow European Guideline.
13.	Subject replacements on	Not allowed	Not allowed	Not allowed

	dropout or Withdrawal.			
14.	Washout period	(More than five half-lives of units measured) should be separated according to processing	Appropriate washout period (usually at least 5 terminal half-life).	Follow European Guideline.
15.	Sampling points	12-18 samples; additional samples must be collected at T_{max} to continue with a half-life of up to 3 or more.	At least two samples before the expected T_{max}, 3-4 terminal log-linear phases.	Follow European Guideline.
16.	Pharmacokinetic 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 $t_{1/2}$.
17.	Pharmacodynamics Studies	FDA does not recommend PD studies.	Required in the case of Locally acting product	Follow European Guideline.
18.	Strength of the dosage form	Single Dose fasting and Fed study: Higher strength is required. If linear removal at a higher magnitude is documented, a lower magnitude is acceptable. Non-linear elimination is documented at a higher magnitude and a lower magnitude.	Studies of linear and non-linear pharmacokinetics bioequivalence should usually be performed at the highest power.	Follow European Guideline.
Immediate Release Dosage Form:				
1.	Studies to be conducted	two-Period, two-sequence, two-treatments, single-dose cross over study design, single-dose parallel study, single-dose replicate study	Standard design: Randomized, 2-period, 2-sequence single-dose crossover study, Alternative design: parallel, replicated design, Multiple-dose study [alternative to the single Dose study]	Follow European Guideline.
2.	Fasting or Fed condition	Fasting and Fed both Study are required and follow PSG.	Fasting and Fed both Study are required and follow PSG.	Fasting and Fed both Study are required and follow PSG.
3.	Bracketing approach	Product-specific guidance to be followed.	Two strength is needed for BE assessment in both study [Fed and fasting].	Follow European Guideline.
4.	pK parameters	C_{max}, T_{max} , AUC_{0-t} , AUC_{0-inf}	Single dose: AUC(0-t), AUC(0-∞), C_{max} ,$t_{max,}$ $AUC_{(0-72h)}$ and $t_{1/2.}$ Steady State: steady state, $AUC_{(0-t)}$, Cmax,ss, and tmax,ss	Follow European Guideline.
5.	In-vitro testing [Biowaiver]	Biowaiver is possible when BCS Class- drugs	Biowaiver is possible when BCS Class- I & Class-III drugs	Follow European Guideline.
Modified Release Dosage Form:				
1.	Studies to be conducted	two-Period, two-sequence, two-treatments, single-dose cross over study design, single-dose parallel study, single-dose replicate study	randomized, 2-period, 2-sequence single-dose crossover study	Follow European Guidelines.
2.	Fasting or Fed condition	Fasting and Fed both Study are required and follow PSG.	Based on EU SmPC	Follow European Guidelines.
3.	Sprinkle BE Studies	RLD products state that products can be administered sprinkled in soft foods and follow the recommendation for the fasting BE studies.	Follow the recommendation for the Fed BE studies.	Follow European Guidelines.

4.	IVIVC [In Vitro-In Vivo Correlation Studies]	Explain the relationship between in vitro [lysis or drug release] and in vivo [plasma concentration and drug absorption].	Explain the relationship between in vitro [lysis or drug release] and in vivo [plasma concentration and drug absorption].	Follow European Guidelines.

6. Conclusion

A comprehensive study of various parameters between the USA, Europe, and Australia revealed that these three countries follow ICH GCP guidelines. It has been observed that the Harmonization of regulatory requirements for bioequivalence studies has significant differences in policies and procedures related to the determination of bioavailability and bioequivalence.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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