

Harmonization in BABE Studies: A simple approach on Regulatory Aspects

Tamilselvi Manickam^{1*} Ankanagari Srinivas²

1. Quest Life sciences (P) Ltd, MEPZ, Tambaram, Chennai 600 045, India.
2. RRS College of Engineering and Technology, Associate Professor, Department of Biotechnology, Muthangi, Patancheru , Medak Dt, Andhra Pradesh, India – 502300

Corresponding author' Email: manickamtamilselvis@gmail.com Mobile no. 09952067718

ABSTRACT

Bioavailability and bioequivalence studies play a major role in the drug development especially for both new drug products and their generic equivalents. Several approaches to assess Bioequivalence and each regulatory authority have its own regulations for conducting Bioavailability and bioequivalence studies before approving generic products for marketing. Thus, there is a greater need to harmonize the regulatory environment globally for bioequivalence assessment practically so that the drug product marketed in different parts and regions of the world.

Keywords: *BABE studies, harmonization, regulatory aspects.*

INTRODUCTION

Bioavailability (BA) and bioequivalence (BE) studies play a major role in the drug development phase especially for both new drug products and their generic equivalents. Bioequivalence is a strategy to introduce generic equivalents of brand-name drugs (innovator drugs) to lower the cost of medication through proper assessment as directed by the international regulatory authorities. There are several approaches to assess BE and each regulatory authority has its own regulations/guidance for conducting BA/BE studies before approving generic products for marketing in their country. Hence a clear understanding is required of these BA/BE concepts and basic regulatory considerations for conducting BA/BE studies. The importance of assessment of bioequivalence of drug product is influenced by the regulatory environment of the country where the drug is getting marketed. Highly regulated markets have more stringent regulatory policy than countries that are not tightly regulated³. Thus, by developing a consensus or understanding and harmonizing among the regulatory authorities of different countries, both the consumers and producers can be benefited immensely.

NDA & ANDA

For a generic product, it is typically a comparison of a competitive formulation with a reference product. The initial oral formulation for a new drug is frequently used to conduct early human studies of safety and efficacy.

Applications from manufacturers seeking regulatory approval for a new drug (e.g. New Drug Application (NDA)) must furnish exhaustive information about a drug's pharmacokinetics. Manufacturers seeking regulatory approval of competitive (generic) products (e.g. Abbreviated New Drug Application [ANDA]), must provide detailed bioavailability evidence showing head-to-head comparative performance of their product against the innovator's

product. Such trials are fundamentally designed to establish clinical equivalence particularly as it relates to interchangeability or substitutability.¹

Statistical methods are applied to test if the metrics are sufficiently similar to be considered equivalent. Achieve this bioequivalence, the study products' geometric mean ratios (eg. AUC test/AUC reference), as well as their projected 90% confidence intervals for the population mean ratio, must be located within an 80 to 125% window⁴.

(ANDA): Bioequivalence Studies

The design and requirements in, bioequivalence studies are fundamentally satisfied through single dose administrations. The focus is on the rate and extent of absorption of the active ingredient, although some jurisdictions (e.g. FDA) continue to show an interest in the primary active metabolite(s). As a general principle, the studies are designed to test inherent product absorption properties. Thereby, the trials generally specify healthy normal controls that exhibit circumscribed demographics.

Assessment of Bioequivalence

A lot of advances have been made for the past several years in developing various approaches to assess BE through research that would assure high quality interchangeable and affordable drugs.

Bioavailability captures two essential features, namely *how fast* the drug enters the systemic circulation (rate of absorption) and *how much* of the nominal strength enters the body (extent of absorption). Given that the therapeutic effect is a function of the drug concentration in a patient's blood, these two properties of non-intravenous dosage forms are, in principle, important in identifying the response to a drug dose. Onset of response is linked to the *rate* of drug absorption whereas the time-dependent extent of response is linked to the *extent* of drug absorption.

The assessment of BE of different drug products is based on the fundamental assumption that two products are equivalent when the rate and extent of absorption of the test/generic drug does not show a significant difference from the rate and extent of absorption of the reference/brand drug under similar experimental conditions as defined. As per the different regulatory authorities, BE studies are generally classified as:

1. Pharmacokinetic endpoint studies.
2. Pharmacodynamic endpoint studies.
3. Clinical endpoint studies.
4. In vitro endpoint studies.

The most frequent data treatment of above mentioned studies involves analysis of variance using a suitable program such as SAS® (Statistical Analysis System, SAS Institute, Cary, NC) or WinNonlin® (Pharsight Corporation, St. Louis, MO).

Highly Variable Drugs (Nontraditional Study Designs for Proving Bioequivalence)

The number of subjects required for a study can be much higher than normally needed for a typical BE study. Several proposals are available to modify the existing BE criteria for these variable drugs. A potential solution to the problem of highly variable drugs is suggested by the observation that most highly variable drugs have a wide therapeutic index. The proposed approach adjusts the BE limits of highly variable drugs/products by scaling to the within subject variability of the reference product in the study.

The proposed approach will resolve issues in the BE evaluation of highly variable drugs while achieving the regulatory authorities mission by ensuring that all the drugs approved are safe and effective. Thereby securing and expanding opportunities for generic formulations in the future. There is also a need for all national regulatory agencies, especially in the emerging markets to align themselves and update regulatory approval processes, in accordance with the current international thinking on the subject.

The approach of one-size fits all has been relaxed in recent years by various regulatory authorities for drugs which exhibit high variations, i.e. large fluctuations, within individuals. It has been very difficult to determine BE for this class of drugs unless unethically large numbers of volunteers were included in the investigations.

More recently, other data treatments have been popular, which include partial area measurements and exposure metrics including C_{max}/ AUC, especially with highly variable drugs (HVDs), and with drugs having a long terminal t_{1/2}, specialized dosage forms, and/or whose time to C_{max} is considered important (eg, certain analgesics). The adaptation of the BA/BE concept worldwide for over 20 years has enabled the production and approval of quality generic products through profound scientific, technical, and regulatory advances (especially through replicate designs, application of BCS, scaled average BE) by various approaches to assess BE for various complex and special groups of drugs. This continuing success story of BA/BE is based on the contribution to efficacy, safety, and quality by international regulatory authorities, pharma industry researchers, academic researchers, and indeed the efforts from ICH, WHO, and various international conferences.

Add on Subjects

Major regulatory agencies have recently encouraged additional design features which permit the later addition of subjects. If the analysis indicates that the calculated 90% confidence intervals of the PK parameters are moderately outside the regulatory BE interval of 80% to 125% then a second group of subjects could be investigated. A combined analysis of the two groups could be performed; these would apply a modified structure of the statistical computations and, again, adjusted significance levels. Health Canada accepts also a simple add-on of at least 12 subjects]. The structure of the statistical analysis should be modified and the level of significance should be 0.025 instead of 0.05. (FDA), require that evidence of average bioequivalence (BE) (in terms of the Extent and rate of drug absorption) be provided through the conduct of bioequivalence studies.² For the assessment of average bioequivalence, a standard two sequence, two-period (2x2) crossover design is usually employed.

Drug interchangeability and Switchability

Drug switchability, on the other hand, involves the switch from a drug product (either a brand-name or generic drug product) to an alternative formulation (again, either a generic or the brand-name drug product) within the same subject whose concentration of the drug product has been titrated to a steady, efficacious and safe level. It is a safety concern whether these generic drug products can be used interchangeably.

Current regulations do not indicate that two generic copies can be used interchangeably even if both of them are bioequivalent to the same brand-name drug. Bioequivalence between generic copies of a brand-name drug is not required. Thus, one of the controversial issues is whether these approved generic drug products can be used safely and interchangeably.

Theoretically, the potential difference between two generics could be about twice as large as what is allowed between a generic and the originator's formulation. The reason is that regulatory agencies worldwide require that the reference drug to which the comparison is made should be the originator's formulation.

One size to fit all criterions

In the past several decades, one size-fits-all criterion has been challenged and criticized by researchers. It was suggested that flexible criteria in terms of safety (upper bioequivalence limit) and efficacy (lower bioequivalence limit) should be developed based on the characteristics of the drug, its therapeutic window and intrasubject variability.

The approach of one size-fits-all has begun to dissipate in recent years. For instance, in some jurisdictions such as Europe, Canada, and recently also in the United States, narrower BE limits have been proposed for drugs with narrow therapeutic windows.

However, FDA has maintained its usual requirement for these drugs with BE limits to be between 80% and 125% even though it has recently indicated a reconsideration of the issue

Harmonized approaches to bioequivalence assessment

Due to significant recognition of the BA/BE concept all over the world, tremendous advancements have been made by the FDA as well as various national and international regulatory authorities. In parallel, pharmaceutical industry and academia are also contributing exclusively in the area of assessment of BE. Currently available approaches to determine BE of generic products are largely standardized due to discussion and consensus reached among various stakeholders at numerous national and international meetings, conferences, and workshops (eg, American Association of Pharmaceutical Scientists, Federation Internationale Pharmaceutique). Thus the currently available excellent scientific and regulatory guidance documents are due to the combined efforts of industry, academia, and regulatory scientists.

Every country now has its own individual regulatory authority and guidance for BA/BE studies, and the magnitude of assessment of BE of drug product is influenced by the regulatory environment of the respective country of marketing. In the United States, the FDA approves and grants marketing authorization of generic drugs by applying the regulatory requirements provided in the Code of Federal Regulations (CFR).

The magnitude of regulatory influence is often dictated by the availability of resources, expertise, and lack of regulation or its implementation. Thus there is a greater need to harmonize the regulatory environment globally for BE assessment as far as practicable so that the drug product marketed in different parts and regions of the world would have optimum drug product quality in terms of interchangeability. In the recent years, some significant progress has been made towards harmonization; in addition some regulatory authorities are also in the process of cooperating with their counterparts from other countries to harmonize the regulatory requirements while streamlining their own regulatory requirements⁵.

WHO has made remarkable progress specifically in developing international consensus on the regulatory requirements for assessing BE for marketing authorization of multisource pharmaceutical products for interchangeability, selection of comparator product for BE assessment and other related regulatory documents. Apart from the ICH and WHO other European and Asian organizations (national and international) are actively involved in harmonization efforts for assessing of BE and improving the quality of pharmaceutical products globally.

In the recent years, some significant progress has been made towards harmonization. The regulatory authorities are also in the process of cooperating with the counterparts of other countries to harmonize the regulatory requirements while streamlining their own regulatory requirements. Leader among them is ICH, it has primarily focused on developing guidelines for standardizing and harmonizing the regulatory requirements, primarily for the chemistry and manufacturing control, safety, efficacy aspects of new drug product quality. In addition, it has developed specific documents for content and format of drug product dossier.

CONCLUSION

Regulatory approaches for evaluating therapeutic equivalence of multisource (or generic) drug products are differ from country to country. Harmonization of these approaches may decrease the number of in vivo bioequivalence studies and avoid unnecessary drug exposure to humans. Global harmonization for regulatory requirements may be promoted by a better understanding of factors underlying product performance and expectations from different regulatory authorities. Existence of these regulations is to guarantee the safety and efficacy of the drugs and there by protecting the end users and consumers⁶. However to date, none of the regulatory have not been completely adopted or accepted by all the regulatory agencies even by those involved in ICH projects. Since pharma work impacts human beings across the globe international agencies have made some effort to harmonize the regulations and guidelines governing this industry. The trend in near future appears towards achieving the appropriate choice of clinically relevant bioequivalence range based on therapeutic ranges, rate of absorption metrics, designs to resolve the issue of intra and inter subject variability.

ACKNOWLEDGEMENTS:

We thanks to Mr. Narayana kumar for giving his valuable suggestions while preparing this article.

BIBLIOGRAPHY

1. Chen ML, Shah VP, Crommelin DJ, Shargel L, Bashaw D, Bhatti M, Blume H, Dressman J, Ducharme M, Fackler P, Hyslop T, Lutter L, Morais J, Ormsby E, Thomas S, Tsang YC, Velagapudi R, and Yu LX. Harmonization of regulatory approaches for evaluating therapeutic equivalence and interchangeability of multisource drug products: workshop summary report. *AAPS J.* 2011 Dec; 13(4):556-64.
2. Latha S (2011) Nontraditional Study Designs for Proving Bioequivalence. *J Bioequiv Availab* 3: ix-000. doi:10.4172/jbb.100000e9
3. Kamal K. Midha, and Gordon McKay Bioequivalence; Its History, Practice, and Future *AAPS J.* 2009 December; 11(4): 664–670.
4. Shubha Rani, and A Pargal. Bioequivalence: An overview of statistical concepts .*Indian Journal of Pharmacology:* 2004 36 (4): 209-216.
5. Shaik Mastan, Thirunagari Bhavya Latha, Sathe Ajay, The basic regulatory considerations and prospects for conducting bioavailability/bioequivalence (BA/BE) studies – an overview 2011 (1): 1 – 25.
6. Michael Zhou, Regulated Bioanalytical Laboratories Technical and regulatory aspects from global perspectives. *Technical and regulatory aspects of Bioanalytical Laboratories* Chapter 5 copy right ©2011 by John Wiley & Sons, Inc, Hoboken, New Jersey.