

Bioequivalence Testing - Industry Perspective

Akula Thukaram Bapuji*, Hamsa Lakshmi Venkata Ravikiran, Meda Nagesh, Syed Syedba, Datla Ramaraju, Chinnapu Reddy Jayaprakash Reddy, Sreedasyam Ravinder, Rosi Reddy Yeruva and Sutirtha Roy

Clinical Pharmacology Department, Aurobindo Pharma Limited, Survey No. 313, Bachupally Village, Quthubullapur Mandal, Hyderabad – 500090, India

Abstract

Generic drugs are cost effective alternatives for the brand name drugs and the savings are estimated in the average \$8 to \$10 billion a year. Over the years the prescription of generic drugs has increased from 19% to 60-70% (1984: 19% & 2009- 60-70%). Bioequivalence testing is playing a vital role in generic drug development.

But to make a generic drug enter in to a regulated market a company has to meet the stringent criteria in the same way as innovative drugs. But the criterion's set forth by the regulatory agencies are not always very descriptive and entrepreneur friendly. The prevailing fierce competition also makes the manufacturers to keep low prices. In order to keep the tight price schedule for generic drugs one must have a clear picture on bioequivalence studies from industry perspective. There are some issues constantly faced by the industry for proper conduct of the BA/BE studies.

The review article describes current regulatory requirements from various regulatory agencies and its impact on industry while designing a bioequivalence study and also highlights some of the common areas, which need to be addressed or commented upon.

It is the time for industry to partner with regulatory agencies to make bioequivalence studies and intern development of generic drugs more cost effective.

Keywords: Bioequivalence; Generic drugs; Highly variable drugs; Narrow therapeutic index drugs

Abbreviations: ANDA: Abbreviated New Drug Application; AUC: Area under the Curve; BA: Bioavailability; BE: Bioequivalence; CFR: Code of Federal Regulations; EMEA: European Medicines Agency; FDA: Food and Drug Administration; GCP: Good Clinical Practice; GLP: Good Laboratory Practice

Introduction and Background

The story of generic drugs starts in the 1930's. In 1984 Hatch-Waxman Amendments to Federal Food, Drug and Cosmetic Act (FD&C Act) came and it was considered one of the most successful pieces of legislation ever passed and created the generic drug industry (Gerald et al., 1999; Drug Price Competition and Patent Term Restoration Act of 1984).

A generic drug is the same as a brand-name drug in dosage, safety, strength, quality, route of administration, indication and to be bioequivalent (BE) with the innovator. When a generic drug is claimed bioequivalent to a brand-name drug, it is assumed that they are therapeutically equivalent. Bioequivalence testing is very important for regulatory filing. This data forms the important component for Abbreviated New Drug Application submissions. Bioequivalence plays a vital role in generic drug development (Information for Consumers).

Generic drugs are cost effective alternatives for the brand name drugs and saving an estimated average \$8 to \$10 billion a year (Lauren et al., 2009; Information for Consumers). Over the years the prescription of generic drugs has increased substantially (1984: 19% & 2009- 60-70%) (IMS health; Information for consumers). When it comes to price, there is a big difference between generic and brand name drugs. Previously the cost of generic drug is 50% of the brand name drug. At present on average, the cost of a generic drug is 80 to 85% lower than the brand name product. The prevailing fierce competition also makes the manufacturers to keep low prices (Shukla et al., 2009).

The generics have to be developed and tested in human subjects by following stringent GCP/GLP standards. From industry point

of view, there is a need to conduct bioequivalence studies at an allowable cost to have an effective generic development program in a scientifically acceptable standard. In order to achieve this from time to time various regulatory agencies have issued guidance's to bring more clarity and uniformity for conducting Bioavailability (BA) / Bioequivalence (BE) studies. For example FDA is issuing product specific BE guidance's to bring a uniform standard. In the European Union, no such specific guidance except a general one.

These are some of the important, present recommended and effective guidelines from European Union (EU) & USA according to year. Regulations were established for BE in 1975, finalized and became effective in 1977. In 90's Guidelines were given by the all the regulatory agencies to bring clarity for the industry.

- 1977: Regulations were finalized and became effective (Code of federal regulations)
- 1984: Hatch-Waxman Amendments to Federal Food, Drug and Cosmetic Act (FD&C Act): Created the generic drug industry
- 1999: EMEA- NfG (Note for Guidance) on Modified Release Oral and Transdermal Dosage Forms.
- 2001: FDA- Guidance on Statistical Approaches
- 2002: EMEA- NfG on the Investigation of BA & BE
- 2003: FDA- BA & BE Guidance - General Considerations (Oral dosage forms)

***Corresponding author:** Akula Thukaram Bapuji, Clinical Pharmacology Department, Aurobindo Pharma Limited, Survey No. 313, Bachupally Village, Quthubullapur Mandal, Hyderabad – 500090, India, Tel: 91-40-23040261, 91-9848732447; Fax: 91-40-23040262, E-mail: bapuji@urobindo.com

Received July 28, 2010; **Accepted** August 26, 2010; **Published** August 26, 2010

Citation: Bapuji AT, Venkata Ravikiran HL, Nagesh M, Syedba S, Ramaraju D, et al. (2010) Bioequivalence Testing - Industry Perspective. J Bioequiv Availab 2: 098-101. doi:10.4172/jbb.1000039

Copyright: © 2010 Bapuji AT, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.



- 2006: EMEA- Evaluation of Bioequivalence of HVDs (Highly variable drugs), EMEA- Questions & Answers on the Bioavailability and Bioequivalence
- 2007: FDA- Individual Product Bioequivalence Recommendations
- 2008: FDA- Evaluation of a Scaling Approach for the Bioequivalence of Highly Variable Drugs (Haidar et al., 2008).
- 2009: Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics
- 2010: EMEA- Guideline on The Investigation of Bioequivalence

These regulations have helped the Pharma industry to pump in more generics. However the perceptions of industry on some of the following important areas are still need to be highlighted.

Selection of reference product & differences in innovator PK behavior

Pharmaceutical companies develop products based on their business plans and development of generics for USA and EU gets the priority.

Reference Listed Drug (RLD): A reference listed drug (21 CFR 314.94(a)(3)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA (Information for consumers)

In most countries, the RLD is generally the innovator drug product ("Brand"), which is marketed on the basis of a full dossier that includes chemical, biological, safety, clinical efficacy, labeling, etc. A standard RLD may avoid possible significant variations among generic drug products and their brand name counterparts (Leon et al., 2009).

Selection of Reference product has been a constant issue that the industry is always facing, because the RLD or brand name counterpart used to establish therapeutic equivalence may vary in different domestic markets.

In general FDA suggests highest strength as RLD or as per individual product recommendations where as for EU generally highest strength or the choice should be justified if lower strength is used based on safety, linearity and dose proportionality, but for selection of dose and strength one need to depend on the literature but lack and validity of the literature (NfG on the Investigation of Bioequivalence- CPMP/QWP/EWP/1401/98 Rev. 1).

For EU submission the choice of reference product should be justified by the applicant. If there is a significant difference between the reference products originating from the same manufacturer. Concerned member states may request information from the first member State on the reference product, namely on the composition, manufacturing process and finished product specification. The whole process may require additional bioequivalence studies using the product registered in the concerned member state as the reference product. (NfG on the investigation of Bioavailability and Bioequivalence- CPMP/EWP/QWP/1401/98).

As per the present scenario generic product development by the entrepreneur is carried out for all the markets simultaneously in order to reduce cost. Recently EU has come out with a relatively better option to reduce the developmental cost of generic product like same test product can be compared against two references in a 3 way design, but in case of failure with any one of the innovator, industry has to go back to reformulation (NfG on the Investigation of Bioequivalence- CPMP/QWP/EWP/1401/98 Rev. 1).

If we tweak our objective that in the global marketplace, all generic, multisource, drug products should be bioequivalent and therapeutic equivalent to a single, standard RLD to avoid possible significant variations among generic drugs and their brand name counterpart, it could possibly reduce the burden of generic entrepreneur. But in order to achieve it we need to come out with an universal reference (Leon et al., 2009).

BE for HVD

Development of ANDAs for highly variable drug is the major concern for the generic drug industry. Drugs and drug products that exhibit high within-subject variability in Cmax and AUC present a challenge for the design of BE studies. For example, a drug with a variability of 50% would require a study in 100 subjects to demonstrate the equivalence of the reference to itself. So development of study designs that would allow demonstration of bioequivalence with a smaller number of subjects was needed. (Marier et al., 2008)

From time to time different regulatory has come with different approaches to control HVDs like sequential (adaptive) designs, add-on studies etc.

FDA created working group to evaluate the scaling approach. Committee for Medicinal Products for Human Use (CHMP) came out with and concept paper for evaluation of bioequivalence of highly variable drugs and drug products. (Background information for Advisory committee 2004; CHMP- Concept paper for guidance on the investigation of bioavailability and bioequivalence of highly variable drugs)

Recently FDA working group proposed the evaluation of a scaling approach for the bioequivalence of highly variable drugs based on the variability of Cmax and AUC. Industry is trying to utilize the concept for HVDs for proving bioequivalence. Individual recommendations for scaled average bioequivalence for some molecules are already available from FDA (Haidar et al., 2008).

EMEA guidance (2010) proposed a more dynamic 90% CI for HVDs for Cmax, as per which acceptance criteria for Cmax can be widened to a maximum of 69.84 – 143.19% based on maximum variability of 50%. Though it is a similar kind of approach but still need more clarity with respect to reference variability > 50% Eg: Lansoprazole (>70%) & Atazanavir (>60%) and it is limited for Cmax Eg: Risedronate, Ibandronate etc. (NfG on the Investigation of Bioequivalence- CPMP/QWP/EWP/1401/98 Rev. 1)

Narrow therapeutic index drugs (NTIDs)

NTIDs pose a special problem in meeting the regulatory specific bioequivalence criteria.

A list of so-called narrow therapeutic index drugs was prepared by the Center for Drug Evaluation and Research (CDER). The list is in the "Scale-Up and Post-Approval Changes for Intermediate Release Products" (Guidance for Industry 1995).

Whereas as per EMEA It is not possible to define a set of criteria to categories drugs as NTIDs and it must be decided case by case if an active substance is an NTID based on clinical considerations (NfG on the Investigation of Bioequivalence- CPMP/QWP/EWP/1401/98 Rev. 1). Even there are not set criteria for Health Products and Food Branch (HPFB) to categorize drugs as NTIDs except for some molecules provided in the list under Bioequivalence Requirements: Critical Dose Drugs (Guidance for Industry- HPFB; Report C: Report on Bioavailability of Oral Dosage Formulations).

The current HPFB criteria for a NTID require that the 95% confidence interval (CI) of the test-to-reference ratio (T/R) of AUC_{0-t} and C_{max} fall completely within the 80-125% where as acceptance interval for NTIDs in case of EU is 90.00-111.11%. This differs from the FDA criteria, which require that the 90% CI of AUC_{0-t} and C_{max} to only fall within the 80-125% boundary (Report C: Report on Bioavailability of Oral Dosage Formulations; Guidance for Industry- General consideration 2003; NfG on the Investigation of Bioequivalence-CPMP/QWP/EWP/1401/98 Rev. 1).

At some point in the future, industry seeks for an appropriately harmonized guidance developed based on this criterion to provide guidance to assess bioequivalence of NTIDs, including a universal listing of NTIDs.

Evolution of guidance's – other side

Industry is always getting the benefit due to regular review and updates by the regulatory for their requirement. On the contrary industry is also facing little difficulty due to the transition phases arising out of this. For instance industries are getting queries from regulatory based on the future perspective, which is very difficult to justify.

Which could be better understood by the following examples:

Draft EMEA guidance (CHMP- Guideline on the investigation of bioequivalence; CPMP/EWP/QWP/1401/98 Rev.1:2008) says, "In case the pro-drug or active metabolites display non-linear pharmacokinetics, it is recommended to demonstrate bioequivalence for the main active metabolite. In such case, the parent compound does not need to be measured provided that it is inactive from efficacy and safety perspectives." Based on this studies were conducted on valacyclovir by measuring aciclovir. But as per the final guidance EMEA (NfG on the Investigation of Bioequivalence- CPMP/QWP/EWP/1401/98 Rev. 1), we need to measure parent compound Valaciclovir.

As per Q & A (CHMP- EWP-PK: Questions & Answers on the Bioavailability and Bioequivalence Guideline EMEA/CHMP/EWP/40326/2006) and Draft EMEA guidance (CHMP- Guideline on the investigation of bioequivalence; CPMP/EWP/QWP/1401/98 Rev. 1: 2008), for all immediate release products standard breakfast is recommended for fed study until unless no Summary Product of Characteristics (SPC) recommendation. Whereas as per the final EMEA (NfG on the Investigation of Bioequivalence- CPMP/QWP/EWP/1401/98 Rev. 1) guidance, high fat breakfast is recommended until unless no SPC recommendation.

Studies conducted during this period using the concept of Q & A (2006) and Draft (2008) will invite definite enquiries from member states. Because of the change in review process, industry is getting affected. So more studies and more cost need to be incurred.

BE in different races/ special populations and differences in PK

Genetic variations among racial/ ethnic groups can alter drug disposition. For example, genetic polymorphism of the human multidrug resistance (*MDR1*) gene has been shown to cause significant variability in P-glycoprotein (P-gp) expression between racial groups. White persons, who predominantly carry the T/T or C/T genotype, express less P-gp in intestinal epithelial cells than do black persons, who predominantly carry the C/C or C/T genotype. Thus, these factors must be considered potential sources of variability in drug pharmacokinetics parameters (Angela et al., 2007). But in case of bioequivalence studies with crossover design the effects are

minimal and not significant when test and reference is given to same individual population.

Due to the above reasons USA & EU are accepting bioequivalence studies from non-USA and non-EU population. But for countries like Japan, Korea and Mexico, bio studies are required to be conducted with their own population which intern is increasing the cost, time and resources for generic drug developments.

Pharmacokinetics of drugs are different in different population (races) because of the different geographical location, food habits and the metabolic pattern; but when we talk BE, and especially when we talk crossover this should not too much of an issue. Races, different geographical location, food habits and the metabolic pattern etc generally are not believed to affect T/R. Though studies from other populations are generally well accepted in USA and EU; frequent queries are being faced by industry from various regulatory due to different pharmacokinetics obtained in BE study when compared with available literature in other population, some times even questioning the validity of study as well.

Similar problem is associated when bioequivalence study is required to be conducted in special populations; for example BE study for Entacapone are need to be conducted in subjects of age group >60 years and above (OGD Individual product recommendation, 2008).

The BE studies should normally be performed in healthy volunteers unless safety warranties. Study in healthy volunteers, is adequate to detect formulation differences and allow extrapolation of the results to populations for which the reference product is approved (the elderly, children, patients with renal or liver impairment, etc.).

There is a wide experience that two formulations that were bioequivalent in one study population will also be bioequivalent in other populations (Rhodes, 1995). Generic drug developers are still behind the exact reason for proving BE in special population, particularly when it is a crossover design.

Fed study waiver: US-FDA

As per Food-effect Bioavailability and Fed Bioequivalence guideline "In addition to a BE study under fasting conditions, we recommend a BE study under fed conditions for all orally administered immediate-release drug products, with the following exceptions:

- When both test product and RLD are rapidly dissolving, have similar dissolution profiles, and Biopharmaceutics Classification System (BCS) Class I or
- When the DOSAGE AND ADMINISTRATION section of the RLD label states that the product should be taken only on an empty stomach, or
- When the RLD label does not make any statements about the effect of food on absorption or administration." (Food-Effect: Guidance for Industry, 2002)

But if we take the example of escitalopram and bisoprolol, both these drugs belongs to class-I and there are no special recommendation about the dosage and administration with regards to food. The absorption of both bisoprolol & escitalopram is not affected by food. Still FDA recommends biostudies to be conducted under both fast and fed conditions. The developmental cost for generic will drastically reduce if generic developer can claim bio waiver for fed study for these kinds of molecules (OGD Individual product recommendation).

Significant sequence/treatment/period effects in BE study

When we carry out the ANOVA, we will not look for significant effects for treatment, sequence or period. The assumptions underlying the crossover designs dictate that these effects are non-significant because they invalidate the trial.

Sequence effects: The sequence effects measure the differences between the groups of subjects defined by their sequences. A true sequence/carry-over is *highly unlikely* in a BE study if the study is performed in healthy subjects, the drug is not an endogenous entity, an adequate washout period (no pre-dose concentrations) was maintained and an appropriate design and analysis was employed. So testing for a sequence effect in a 2,2 crossover BE study testing for a sequence effect is futile.

Treatment effects: A significant effect for treatment can simply be ignored. A significant treatment effect can be present when the treatment mean square is small. In other words the ANOVA procedure carried out is nothing but the evaluation identical to the power approach, so it can be said that the significant difference can occur at the moment the variability is low or the number of volunteers are sufficiently high. The decision of bioequivalence is based on the Schuirmann test and when the 90% confidence interval is within the equivalence limit, there should not be anything to worry about. Basically we just employed too many volunteers.

Period effects: A significant period effect is caused by the fact that in one of the two periods, the plasma levels (and AUC) are higher/lower than in the other. The causes may be many. There are still discussions on the meaning of significant period effects. When both treatments are affected in an equal way their relationship does not change and hence the comparison between the two is valid. But practically speaking the cause of a period effect is not known and the proof of equal change becomes difficult (Bioequivalence and generic medicine)

It is already published that Testing for a sequence effect in a 2x2 cross-over study (Grizzle et al., 1965) is statistically flawed and therefore simply futile (Freeman et al., 1989), significance of treatment effects can simply be ignored for BE study and there are no possible reasons for significant period effects. Still industries are facing many enquiries followed by rejection of BE study by different regulators due to significant effects in some cases whereas in certain other cases though there are significant effects it is simply being ignored by the regulators.

Conclusion

Even after the tremendous efforts by the regulatory agencies on Bioequivalence some fine-tuning is required in bringing more clarity and uniformity which will be helpful for the generic drug industry in order to reduce the number of studies, for example Standards for steady state in case of modified release (MR) formulation. Multiple dose study is not a requirement for MR Products in USA (ANDAs). Coming to EU, multiple dose study is required where as it is less sensitive in detecting formulation differences when compared with single dose studies. Outlier challenging or re-dosing studies concept is not clear in any of the guidances. By making these fine tunings we can reduce the time, cost and unnecessary exposure of healthy subjects to medicines and finally to market the quality generic drug products.

It is time for industry to partner with regulatory to make bioequivalence studies acceptable and further develop generic drug products in a cost effective manner.

References

1. Background Information for Advisory Committee Meeting On April 14, 2004; Bioequivalence Requirements for Highly Variable Drugs and Drug Products.
2. Bioequivalence and generic medicine; Piter Zanen.
3. CHMP- Concept paper for an addendum to the note for guidance on the investigation of bioavailability and bioequivalence: evaluation of bioequivalence of highly variable drugs and drug products: EMEA/CHMP/EWP/147231/2006.
4. CHMP- EWP-PK: Questions & Answers on the Bioavailability and Bioequivalence Guideline EMEA/CHMP/EWP/40326/2006.
5. CHMP-Draft guideline on the investigation of bioequivalence; CPMP/EWP/QWP/1401198 Rev. 1: 2008.
6. Code of Federal Regulations. Title 21 food and drugs chapter I- food and drug administration department of health and human services subchapter d- drugs for human use. PART 320- Bioavailability and Bioequivalence requirements.
7. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 1984 Stat. 1538 (codified as amended in scattered sections of 21 & 35 U.S.C.).
8. Food-Effect Bioavailability and Fed Bioequivalence Studies (2002) Guidance for Industry.
9. GRIZZLE JE (1965) The two period change over design and its use in clinical trial Biometrics. 21: 467-480.
10. Guidance for Industry (November 1995) Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing and *In Vivo* Bioequivalence Documentation.
11. Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products (2003) General Considerations.
12. Guidance for Industry- HPFB Bioequivalence Requirements: Critical Dose Drugs.
13. Höfer L, Huynh M, Lindsey WT (2009) Substitution of Generic Drugs for Brand Name Drugs JPSW November/December.
14. IMS health, Banc of America Securities LLC estimates.
15. Information for Consumers (Drugs); FDA U.S Food and drug administration.
16. Marier JF, Brunet JS (2008) Critical Path Opportunity for the Development of Generic Products Pharsight (Online source: http://www.pharsight.com/library/sign_in/Critical%20Path%20Opportunity%20for%20the%20Development%20of%20Generic%20Products.pdf).
17. Shargel L; International Reference Listed Drug Product; AAPS Annual Meeting 10th November 2009. (Online Source: http://mediaserver.aapspharmaceutica.com/meetings/09AM/Slides/11.10.09_Tue/403%20B/1400/Leon%20Shargel.pdf).
18. Mossinghoff GJ (1999) Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process. Food Drug Law J 54: 187-194.
19. NfG on the investigation of Bioavailability and Bioequivalence- CPMP/EWP/QWP/1401/98.
20. NfG on the Investigation of Bioequivalence; CPMP/QWP/EWP/1401/98 Rev. 1.
21. Shukla N, Sangal T (2009) Generic Drug Industry in India: The Counterfeit Spin. J INTELLECT PROP RIGHTS 14: 236-240.
22. OGD Individual product recommendation- Guidance on Entacapone; Finalized May 2008.
23. Freeman PR (1989) The performance of the two-stage analysis of two treatment, two period cross-over trials. Stat Med 8: 1421-1432.
24. Report C: Report on Bioavailability of Oral Dosage Formulations, not in Modified Release Form, of Drugs Used for Systemic Effects, Having Complicated or Variable Pharmacokinetics (1992) Health Canada.
25. Rhodes CT (1995) Generic substitution: Does interchangeability mean equality of all functional relevant attributes. Clin Res Reg Affairs 12: 267-272.
26. Haidar SH, Makhilouf F, Schuirmann DJ, Hyslop T, Davit B et al. (2008) Evaluation of a Scaling Approach for the Bioequivalence of Highly Variable Drugs. AAPS J 10: 450-454.
27. Sansone-Parsons A, Krishna G, Simon J, Soni P, Kantesaria B, et al. (2007) Effects of Age, Gender, and Race/ Ethnicity on the Pharmacokinetics of Posaconazole in Healthy Volunteers. Antimicrob Agents Chemother. 51: 495-502.

