Review Article

Biowaivers - an updated review

Abilash. N*, Chandramouli. R
Department of Quality Assurance, Krupanidhi College of Pharmacy, #12/1, Chikkabellandur, Carmelaram Post, Varthur Hobli, Bangalore - 560035, KA

DOI:10.18579/jpcrkc/2017/16/3/118768

Received on: 07/03/2017
Revised on: 04/05/2017
Accepted on: 18/08/2017

Corresponding author:
Abilash. N
Department of Quality Assurance,
Krupanidhi College of Pharmacy
#12/1, Chikkabellandur,
Carmelaram Post, Varthur Hobli,
Bangalore - 560035, KA, India
abilpreethu@gmail.com

ABSTRACT

PURPOSE: A Biowaiver has been regarded as an official approval of the waiver for conducting a bioequivalence study in the context of an application for drug approval process. Bioequivalence is an important parameter in the process of drug development that is needed to be performed when there is a change in the formulation of dosage form.

Approach: The approach of biowaivers is necessary to waive a complete and systemic Bioequalence study, which as a fast track approach to boost the drug development process.

Findings: This review mainly discusses about the criteria for Biowaivers, requirements for a BCS based biowaiver study, conditions to grant the BCS based biowaiver, Applications, limitations, supporting data for Biowaivers.

Conclusion: BCS biowaiver studies in preparing a submission for worldwide filing to satisfy US, European, and emerging market regulators. It is hoped that the availability of BCS Class I and Class III biowaivers in multiple jurisdictions will encourage more sponsors to request waivers of *in vivo* bioavailability/bioequivalence testing using the BCS approach.

Keywords: Biowaivers, BCS class, BABE studies, Drug development.

INTRODUCTION

Biowaiver

Biowaivers are considered as the waivers of clinical bioequivalence studies[1,2]. Bioequivalence studies are as vital concern in drug development process, which are required for small changes in drug products that develop during drug development to ensure that the dosage forms prove to be safe and effective[3].

"Biowaiver" means avoiding time consuming and costly pharmacokinetic studies and using in vitro dissolution test as a surrogate test to evaluate the bioequivalence of a test and reference product.

Advantages of biowaivers:

- Circumvent expensive and sometimes unethically questionable human testing.
- Reducing time in bringing product to the market.
- Reduce product cost[4].

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)[5,6,7]

Class I (High Permeability, High Solubility)

These compounds are well absorbed and their absorption rate is usually higher than excretion. Drugs exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid

then gastric emptying rate becomes the rate determining step. Examples: Metoprolol, Diltiazem, Verapamil, Propranolol

Class II (High permeability, Low solubility)

The bioavailability of these products is limited by their solvation rate. Drugs have a high absorption number but a low dissolution number. The absorption for class II drugs is usually slower than class I and occurs over a longer period of time.

Examples: Danazol, Ketoconazole, Glibenclamide, Mefenamic acid, Nifedipine and Itraconazole.

Class III (Low permeability, High solubility)

The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time then class I criteria can be applied. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is an aspect to alteration of physiology and membrane permeability rather than the dosage form

factors. Examples: Cimetidine, Acyclovir, Neomycin B, and Captopril.

Class IV (Low permeability, Low solubility)

These compounds have a poor bioavailability and not good absorbed over the intestinal mucosa properly. Such drugs show evidence of a lot of problems for effective oral administration. Examples: Hydrochlorothiazide and Taxol.

Criteria for Biowaivers[8,9]

a. If the drug product is a Parenteral solution intended solely for administration by injection or an ophthalmic or otic solution.

b. If the drug product contains same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application.

Requirements for a BCS-based biowaiver study include:[10]

a. Dissolution Test in 3 different media (in 900 ml and at 37°C) which are:

   Buffer pH 1.2, simulated gastric fluid without enzymes or 0.1N Hcl.

   Buffer pH 4.5.

   Buffer pH 6.8 or simulated intestinal fluid without enzymes.

b. 12 samples in each media, paddle rotating at 50 rpm or basket at 100 rpm.

c. Sampling times are 10, 15, 20, 30, 45 and 60 minutes.

d. The profiles of the test and reference products must be similar in all three media.

e. The products are similar if the similarity factor f2 $\geqslant$ 50 and both products show $\geqslant$ 85% dissolution in 15 min.

CONDTIONS OF GRANT FOR BCS-BASED BIOWAIVERS

Dosage forms containing active pharmaceutical ingredients (APIs) which are highly soluble and highly permeable (i.e. BCS class 1), and are rapidly dissolving are eligible for a biowaiver based on the BCS, provided:

1. The dosage form is rapidly dissolving (i.e. no less than 85% of the labeled amount of the API dissolves in 30 minutes)

2. The dissolution profile of the multisource product is similar to that of reference product at pH 1, 2; pH 4, 5; and pH 6, 8 buffer using the paddle method at 75 rpm or the basket method at 100 rpm and meets the criteria of dissolution profile similarity, f2 $\geqslant$ 50 (or equiv alent statistical criterion)[11,12]. If both the reference and the multisource dosage forms are very rapidly dissolving, i.e. 85% or more dissolution at 15 minutes or less in all 3 media under the above test conditions, thetwo products are deemed equivalent and a profile comparison is not necessary[11,13].

APPLICATIONS OF BCS IN BIOWAIVER OF DRUG[14-19]

The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is

approved based on evidence of equivalence other than through *in vivo* equivalence testing. Biowaiver means to obtain waive off for carrying out expensive and time-consuming BA and BE studies. BCS provides biowaiver for Class I, II and III drug with some specifications. This waiver is for both pre- and post approval phases. The USFDA BCS guidance recommends for biowaiver if the drug substance is highly soluble and highly permeable (Class I drugs) or an immediate release drug product. For waiver of an in vivo relative BA study, dissolution should be greater than 85% in 30 minutes in the three recommended dissolution media. When both the test and the reference products dissolve 85% or more of the labeled amount in <15 min, in all 3 dissolution media recommended above a profile comparison is unnecessary.

The drug should not be a narrow therapeutic index drug, excipients used in the dosage form should have been previously used in a FDA approved IR solid dosage forms, the quantity of excipients in IR product should be consistent with their intended function and the drug must be stable in gastrointestinal tract along with the product is designed not to be absorbed in oral cavity are also biowaiver in USFDA BCS guidance documents. BCS-based biowaiver is applicable for immediate-release solid oral dosage formulations containing one or more of the API(s), identified by WHO Pre-qualification of medicines programme (PQP) to be eligible, if the required data ensure the similarity of the submitted pharmaceutical product and the appropriate comparator product. Comparator products used in BCS biowaiver applications should be selected from the current list of WHO PQP recommended comparator products, including the appropriate fixed-dose combination product.

Limitation of BCS[20]

BCS based biowaiver are not applicable for the following:

i. Narrow therapeutic range drug products.

ii. BCS based biowaivers have limited application for the class II drugs and not applicable for class III.

iii. Dosage form meant for absorption in the oral cavity e.g. sublingual or buccal tablets.

iv. Effects of food, absorptive transporters, efflux transporters, and routes of elimination (renal/biliary) were important determinants of overall drug absorption and bioavailability for immediate release oral dosage forms, which are not considered in BCS.

DATA TO SUPPORT REQUEST FOR BIOWAIVERS:

Quantities of data to support a request for biowaivers have to be submitted. The drug substance for which a waiver is being requested should be highly soluble and highly permeable. Sponsors requesting biowaivers based on the BCS should submit the following information to the Agency for Review by the Office of Clinical Pharmacology and Biopharmaceutics (for NDAs) or Office of Generic Drugs, Division of Bioequivalence (for ANDAs)[21].

A. Data Supporting High Solubility The following information should be included in the application:

a) Description of test methods including information on analytical method and composition of the buffer solutions.

b) Information on chemical structure, molecular weight, nature of the drug substance (acid, base, amphoteric or neutral) and dissociation constants (pKa).

B. Data Supporting High Permeability The following information should be included in the application:

a) For pharmacokinetic studies- information on study design and methods used along with the pharmacokinetic data.

b) For direct permeability methods- information supporting the suitability of a selected method that encompasses a description of the study method; criteria for selection of subjects, animals or epithelial cell line; drug concentrations in the donor fluid.

c. Data supporting rapid and similar dissolution for submission of a biowaiver requesting an immediate release (IR) product should be rapidly dissolving.

The following information should be included in the application:

a) A brief description of the IR products used for dissolution testing including information on batch or lot number, expiry date, dimensions, strength, and weight.

b) Dissolution data obtained with 12 individual units of the test and reference products using recommended test methods.

d. Additional Information the manufacturing process used in the production of test product should be described briefly to provide information on the method of manufacture (e.g., wet granulation vs. Direct compression).

a) List of excipients along with amount used and their intended functions should be provided. In addition, excipients used in the test product should have been used previously in FDA-approved IR solid oral dosage forms[22,23].

REFERENCES

1. Kortejarvi H, Urtti A, Yliperttula M.Pharmacokinetic simulation of biowaivercriteria: the effects of gastric emptying, dissolution, absorption and elimination rates. Eur J Pharm Sci. 2007; 30: 155-66.
2. Dressman JB, Nair A, Abrahamsson B, Barends DM, Groot DW, Kopp S, et al. Biowaivers Biowaiver monograph for immediate-release solid oral dosage forms: Acetylsalicylic acid. J Pharm Sci. 2012; 101: 2653-67.
3. Midha KK, Rawson MJ, Hubbard JW. The bioequivalence of highly variable drugs and drug products. Int J Clin Pharmacol Ther 2005 Oct; 43(10):485-98.
4. Kortejarvi H, Urtti A, Yliperttula M. Pharmacokinetic simulation of biowaiver criteria: the effects of gastric emptying, dissolution, absorption and elimination rates. Eur J Pharm Sci. 2007; 30: 155-66.
5. U.S. Department of Health and Human Services. Food and Drug Administration.
6. Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Center for Drug Evaluation and Research (CDER) August 2000 (Available at: http://www.fda.gov/cder/guidance/index.htm).
7. Ku MS. Use of the Biopharmaceutical Classification System in Early Drug Development. The AAPS Journal 2008; 10(1): 208-212Criteria for biowaivers. Accessed at http://www.anapharm. Com/site/upload/site/Generateur/WilliamsRogers.pdf.
8. World Health Organization (WHO) 2006 Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release,solid oral dosage forms Accessed on January 10, 2011 at http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=403.
9. World Health Organization (WHO) 2006 Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms Accessed on January 10, 2011 at http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=403.
10. Guidance for Industry Waiver of in vivo Bioavailability & bioequivalence Studies for immidate release Solid Oral Dosage Forms Based on a Biopharmaceutical Classification System. Accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInfor ation/Guidances /ucm070246.pdf.
11. Guidance for Industry Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Accessed at: http://www.fda.gov/OHRMS/DOCKETS/98fr/3657gd3.pdf.
12. Gupta E, Barends DM, Yamashita E, Lentz KA, Harmsze AM, Shah VP, Dressman JB, Lipper RA. Review of global regulations concerning biowaivers for immediate release solid oral dosage forms. Eur J Pharm Sci 2006; 29: 315-24.
13. World Health Organization. Prequalification of Medicines Programme Guidance Document. General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications. November 2011.
14. World Health Organization. Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability. WHO Technical Report Series 2006; No. 937.
15. European Medicines Agency. Guideline on the Investigation of Bioequivalence, Committee for Medicinal Products for Human Use (CHMP). Doc. Ref.: CPMP/EWP/QWP/1401 / 98 Rev. 1/ Corrected, 2010.
16. Yu LX et al. Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions. Pharmaceutical Research 2002; 19(7): 921-925.
17. Lindenberg M, Kopp S and Dressman JB. Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system. European Journal of Pharmaceutics and Biopharmaceutics 2004; 58(2): 265–278.
18. Polli JE. Summary Workshop Report: Bioequivalence, Biopharmaceutics Classification System, and Beyond. The AAPS Journal 2008; 10(2): 373-379.
19. Yasir M, Asif M, Kumar A, Aggarval A. Biopharmaceutical Classification System: An Account. International Journal of PharmTech Research 2010; 2(3): 1681-1690.
20. World Health Organization (WHO) 2006 Proposal to waive in vivo Bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms Accessed on January 10, 2011 at http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=403.
21. World Health Organization, Additional guidance for organizations performing in vivo bioequivalence studies. World Health Organization:Technical ReportSeries, No. 937, Annex 9, Geneva; World Health Organization: 2006.