

REVIEW ARTICLE

Biowaivers: Criteria and Requirements

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Received 28 Mar 2012; Revised 10 July 2012; Accepted 17 July 2012

ABSTRACT

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. It has been widely accepted that the *in vitro* tests for solubility, permeability and dissolution form the basis of a drug product's classification and qualification for biowaivers. The biopharmaceutics classification system (BCS) is a scientific approach for classifying drug substances based on their dose/solubility ratio and intestinal permeability. BCS has been widely implemented for waiving bioequivalence studies on the basis of the solubility and gastrointestinal permeability of drug substance. Hence, BCS-based biowaiver has become an important and cost-saving tool in approval of generic drugs. The present review critically aims to discuss various criteria and requirements for conducting biowaiver study alongwith various data to support request for biowaivers.

Key words: Biowaiver, Bioequivalence, Biopharmaceutics.

INTRODUCTION

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]. Moreover, bioequivalence has proven even more significant in case of drugs with narrow therapeutic index (NTI). The bioequivalence studies are required for the clinical development of new chemical entities (NCE), when the formulation of the pharmaceutical dosage form has been changed. The *in vivo* pharmacokinetic data can be used as an important constraint for *in vivo* solubility and permeability data^[3,4]. As it is estimated that the *in vivo* bioavailability and bioequivalence studies cost up to \$ 250,000 each and require up to 2 months to complete, whereas, the *in vitro* laboratory tests are rather inexpensive and fast, in which dissolution studies, similarity factor (f₂) profile calculations and report writing represent a large part of the laboratory work^[5]. Hence, it has been widely accepted that the biowaivers typically save time and cost. The U.S. FDA, European

Medicines Agency (EMA) and Japanese Pharmaceuticals alongwith Medical Devices Agency (PMDA), possess biowaiver guidance documents. It has been reported that recent FDA guidance permits the waiver of additional *in vivo* studies for pharmaceutical products that meet specified criteria. Thus, the costly and time consuming *in vivo* studies may be replaced by fast and low cost *in vitro* tests^[6]. Furthermore, the BCS has appeared as a supportive means in product development by evading to the *in vivo* performance of the active substance^[7]. The bio-relevance of the BCS properties and the *in vitro* release are expressed through a correlation between *in vitro* and *in vivo* data. Recently, BCS has been executed for waiving bioequivalence studies on the basis of the solubility and gastrointestinal permeability of drug substance, which can be strategically deployed to save time and resources during generic drug development^[8]. Moreover, BCS has been developed to allow prediction of *in vivo* pharmacokinetic performance of drug products from measurements of permeability and solubility. In addition, the BCS has been adopted as a useful tool for *in vivo* drug

design and development worldwide, and thus, BCS-based biowaiver has become an important and cost-saving tool in generic drug approval process^[7,8]. The present review highlights various criteria and requirements for conducting biowaiver study. In addition, various data to support request for biowaivers has also been discussed in the present review.

CRITERIA FOR BIOWAIVERS

The *in vivo* bioavailability or bioequivalence of the drug product for certain drug products may be self-evident. FDA waives the requirement for the submission of evidence obtained during *in vivo* demonstrating the bioavailability or bioequivalence of these drug products^[9]. The *in vivo* bioavailability or bioequivalence of such drug products may be considered self-evident if the product meets one of the following criteria:

- 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^[9].

Additionally, FDA may waive the requirement for the submission of evidence obtained *in vivo* demonstrating the bioavailability or bioequivalence of the drug products:

- a) If they are highly soluble: Highest dose is soluble in 250 ml at pH 1.2-6.8.
- b) If they are highly permeable: extent of absorption is greater than 85%.
- c) If they are rapidly dissolving: 85% or greater by basket method at 100 rpm or by paddle method at 50 rpm in 900 ml at pH 1.2, 4.5, 6.8^[10].

Moreover, for waiver of bioequivalence test and reference products, they should exhibit similar dissolution profile ($f_2 \geq 50$)^[11].

REQUIREMENTS FOR A BIOWAIVER STUDY

There have been certain requirements for a biowaiver study that include allowance of regulatory authorities like FDA and WHO etc. The drugs should have high solubility and high permeability according to BCS^[12]. However, other classification systems are part of current investigations. The other requirements for a biowaiver study include:

- a) Dissolution Test in 3 different media which are:

- ❖ Buffer pH 1.2, simulated gastric fluid (SGF) without enzymes or 0.1N HCl
- ❖ Buffer pH 4.5
- ❖ Buffer pH 6.8 or simulated intestinal fluid (SIF) without enzymes, all in 900 ml and at 37°C

- 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 $f_2 \geq 50$ and both products show $\geq 85\%$ dissolution in 15 min^[12,13].

In addition, list of products for which *in vivo* bioequivalence studies are not necessary have also been reported which involve:

- a) Injectable, ophthalmic and otic solutions- provided that the active and inactive ingredients are qualitatively and quantitatively same as the reference listed drug.
- b) Oral and topical solutions- provided that differences in inactive ingredients are characterized and do not affect absorption of active ingredient of the product.
- c) Immediate-release drug products with a determination of efficacy. The regulatory authority may request *in vitro* dissolution testing for oral solid dosage forms. Examples include acetaminophen and codeine tablets, folic acid tablets, hydrocortisone cream and ointment, triamcinolone ointment, cytarabine injectable and dacarbazine injectables.
- d) BCS class 1 drugs, e.g., metoprolol^[14,15].

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^[16]. 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).

A. Data Supporting High Solubility

The following information should be included in the application:

- a) 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).
- c) Test results (mean, standard deviation and coefficient of variation) summarized in a table under solution pH, drug solubility (e.g., mg/ml) and volume of media required to dissolve the highest dose strength.
- d) A graphic representation of mean pH-solubility profile ^[17].

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 alongwith 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; description of the analytical method; and the method used to calculate extent of absorption or permeability ^[16,17].
- c) A list of selected model drugs along with data on extent of absorption (mean, standard deviation, coefficient of variation) used to establish suitability of a method; permeability values for each model drug (mean, standard deviation, coefficient of variation); permeability class of each model drug and a plot of the extent of absorption as a function of permeability (mean \pm standard deviation or 95% confidence interval) with identification of the low/high permeability class boundary and selected internal standard.
- d) Information to support high permeability of a test drug substance should include permeability data on the test drug substance; the internal standards (mean, standard deviation and coefficient of variation); stability information, data supporting passive transport mechanism where appropriate; and the methods used to establish high permeability of the test drug substance ^[16,17].

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. The percentage of labeled claim dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent dissolved, range (highest and lowest) of dissolution and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included.
- c) Data supporting similarity in dissolution profiles between the test and reference products in each of the three media using f2 metric ^[18].

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). Moreover, a list of excipients alongwith 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 ^[17,18].

BIOWAIVER REGULATORY GUIDANCE IN VARIOUS COUNTRIES

A. United States

The US biowaiver guidance is based on the widely known BCS system which is briefly described in (Table 1).

Table 1: Biopharmaceutics classification system (BCS)

Class	Description
1	High solubility, High permeability
2	Low solubility, High permeability
3	High solubility, Low permeability
4	Low solubility, Low permeability

High permeability is defined as 90% absorption in tests. However, US allow biowaivers for rapidly dissolving BCS 1 drug products. Rapidly

dissolving means that 85% or more of the dosage is dissolved in 30 minutes in three media, i.e.;

- ❖ 0.1 N HCl or SGF
- ❖ pH 4.5 buffer
- ❖ pH 6.8 buffer or SIF.

Dissolution studies necessary to justify a US biowaiver are performed according to the ICH harmonized dissolution monograph^[6]. A choice of baskets at 100 rpm (apparatus 1) or paddles at 50 rpm (apparatus 2) is made using product data. The media is same as mentioned above for rapid dissolution. 12 units each of test and reference formulation are compared. Evaluations are performed on mean data using f2 calculation with passing criterion ≥ 50 . When comparing the test and reference products, the dissolution profiles should be compared using f2. The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error, and, is a measurement of the similarity in the percent (%) of dissolution between the two curves.

$$f_2 = 50 \cdot \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n \left(\frac{R_t - T_t}{T_t} \right)^2 \right]^{-0.5} \cdot 100 \right\}$$

Two dissolution profiles are considered similar when the f2 value is ~ 50 . To allow the use of mean data, the coefficient of variation should not be more than 20% at the earlier time points (e.g., 10 minutes) and should not be more than 10% at other time points. When both test and reference products dissolve 85% or more of the label amount of the drug in 15 minutes using all three dissolution media recommended above, the profile comparison with an f2 test is unnecessary^[19,20].

B. European Union

Like US, Europe also allows biowaivers for BCS 1 only, whereas, the proposed guidelines permit BCS 1 and 3 biowaivers. Further, unlike US, 85% absorption is used as the permeability limit. However, there is a requirement for rapid drug product dissolution. The proposed guidelines define rapid as 15 min for both BCS classes. The media are slightly different;

- 1) pH 1.0,
- 2) pH 4.6 and
- 3) pH 6.8 buffers.

The proposed guideline changes it to

- 1) pH 1.2 (0.1 N HCl or SGF without enzymes)
- 2) pH 4.5
- 3) pH 6.8 or SIF without enzymes.

Moreover, the dissolution tests or bioequivalence trials are needed when drug product performance could potentially be affected. These cover compositional or processing changes like increased film coating weight, embossing, and

addition of a new test to the drug substance or excipient specifications^[6,19,20].

CONDITIONS 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:

- ❖ the dosage form is rapidly dissolving (i.e. no less than 85% of the labelled amount of the API dissolves in 30 minutes)
- ❖ 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, $f_2 \geq 50$ (or equivalent statistical criterion)^[16,17].

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, the two products are deemed equivalent and a profile comparison is not necessary^[16, 20].

CONCLUSION

BCS is employed to waive *in vivo* bioequivalence testing (i.e. provide "biowaivers") for new and generic drugs. Granting biowaivers under systems such as the BCS, eliminates unnecessary drug exposures to healthy subjects and provides economic relief, while maintaining the high public health standard for therapeutic equivalence. Using the rationale of BCS, it can be argued that biowaivers can also be granted on the basis of standard pharmacokinetic data. If a drug exhibits dose-linear pharmacokinetics and a sufficiently fast dissolution profile, it can be concluded that this drug do not possess any problem related to absorption. Logically, the dissolution profiles of the different formulations should be equal to guarantee bioequivalency. Thus, both BCS and the alternative linear pharmacokinetics approach require an evaluation of dissolution profiles.

REFERENCES

1. Kortajarvi 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.
2. Dressman JB, Nair A, Abrahamsson B, Barends DM, Groot DW, Kopp S, et al.

- 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. García-Arieta A, Gordon J. Bioequivalence Requirements in the European Union: Critical Discussion. *AAPS J* 2012; in press.
 5. Rolli R. Automation of Dissolution Tests for Biowaiver Studies. Accessed at: http://www.dissolutiontech.com/DTresour/0802art/Article_3.html.
 6. Kelly G. Biowaivers in the United States, European Union, and Japan. Accessed on April 2012 at <http://americanpharmaceuticalreview.com/ViewArticle.aspx?ContentID=4155>.
 7. Dahan A, Miller JM, Amidon GL. Prediction of solubility and permeability class membership: provisional BCS classification of the world's top oral drugs. *AAPS J.* 2009; 11: 740-6.
 8. Smetanova L, Stetinova V, Svoboda Z, Kvetina J. Caco-2 cells, biopharmaceutics classification system (BCS) and biowaiver. *Acta Medica (Hradec Kralove).* 2011; 54: 3-8.
 9. Clinical pharmacology and biopharmaceutics review(s). Accessed at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022536s000ClinPharmR.pdf.
 10. Shah VP. BCS-based Biowaiver Potential Impact of Excipients on Drug Absorption Accessed at: http://www.eufeps.org/document/bad_homburg_conf_08061718/Shah.pdf.
 11. Criteria for biowaivers. Accessed at <http://www.anapharm.com/site/upload/site/Gener-ateur/WilliamsRogers.pdf>.
 12. Biowaiver Studies. Accessed at http://www.pharma-test.com/pdfs/dissolutiong/05200760Biowaiver_09.1.0E.pdf.
 13. General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications. Accessed at http://apps.who.int/prequal/info_applicants/be/bw_general_2009february.pdf.
 14. Guidance for Industry "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations." Accessed at: <http://www.fda.gov/cder/guidance/index.htm>.
 15. Science based criteria for bioequivalence *in vivo* and *in vitro*, biowaivers and strategic framework for implementation Accessed at: <http://www.paho.org/english/ad/thse/ev/be-doct-draft-eng.pdf>.
 16. Guidance for Industry Waiver of *in vivo* Bioavailability & bioequivalence Studies for immediate release Solid Oral Dosage Forms Based on a Biopharmaceutical Classification System. Accessed at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf>.
 17. 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>.
 18. Committee for Medicinal Products for Human Use (CHMP). Accessed at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003011.pdf.
 19. Reddy SK, Jamadar LD, Vasantharaju SG, Sreedhar D. Biowaivers for Immediate Release Solid Oral Dosage Forms. *Pharma Times* 2011; 43: 9-11.
 20. 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.