



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203



Human Journals

Review Article

August 2018 Vol.:13, Issue:1

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Biowaiver for Immediate Release Solid Oral Dosage Form: A General Overview

	IJPPR INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH An official Publication of Human Journals	ISSN 2349-7203 
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Submission:	23 July 2018	
Accepted:	30 July 2018	
Published:	30 August 2018	



HUMAN JOURNALS

www.ijppr.humanjournals.com

Keywords: Biowaiver, Biopharmaceutical Classification System, Guidance for biowaiver

ABSTRACT

Biowaiver is a waiver of *in vivo* bioavailability or equivalence by *in vitro* studies. It 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. Food and Drug Administration (FDA), World Health Organization (WHO), European Union on Medicine Agency (EUMA) has allowed certain Active Pharmaceutical Ingredients (APIs) for biowaiver base on the Biopharmaceutical Classification System (BCS). The BCS is a scientific approach for classifying drug substances based on their dose/solubility ratio and intestinal permeability. Biowaiver is possible for APIs of BCS I and some APIs of BCS II and BCS III. This simpler easily implemented *in vitro* studies ensure effective clinical performance. The present review aims to discuss the requirement and different regulator guidance on biowaiver for immediate release solid oral dosage form.

INTRODUCTION

Over the past many years, dissolution testing has evolved into a powerful tool for characterizing the quality of oral pharmaceuticals product. The dissolution test, at first exclusively a quality control test, is now emerging as a surrogate equivalence test for certain categories of orally administered pharmaceutical products (WHO, 2006).

Biowaiver means to get a waive off for doing bioavailability and bioequivalence studies. In 1995 the Department of human health, federal drug agency of the United States of America (HHS-FDA) instigated the BCS with the aim of granting – so-called biowaiver for scale-up and post-approval changes(SUPAC)(WHO, 2005) but later, the biowaiver principle was extended to the approval of the generic products(Dahan et al., 2009). It is considered as the waiver of clinical bioequivalence studies (Dreesman et al., 2012). Instead of conducting expensive and time-consuming *in vivo* studies, a dissolution test could be adopted as the surrogate basis for the decision as to whether the two pharmaceuticals products are equivalent.

BCS was proposed in 1995 by Amidon et al. ((Dahan et al., 2009), it is a scientific work which divides APIs (Active Pharmaceutical Ingredients) into four groups (Yu et al., 2002) (Table 1). The solubility classification of a drug in the BCS is based on the highest dose strength of an immediate release. A drug substance is considered highly soluble when the highest strength is soluble in 250 ml or less aqueous media over the pH range 1-7, otherwise the drug substances are considered to be poorly soluble((Dahan et al, 2009), the permeability classification of drug substance is based on the extent of intestinal absorption of a drug substances in human or indirectly on the measurements of a mass transfer across the luminal intestinal membrane, a drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90 % or higher, otherwise poorly permeable. WHO considered solubility range of pH1.2-6.8 and 85% or more for the permeability (WHO, 2006).

Table 1: BCS classification based on aqueous solubility and intestinal permeability

BCS I High solubility High permeability	BCS II Low solubility High permeability
BCS III High solubility Low permeability	BCS IV Low solubility Low permeability

The requirement for biowaiver (Rohilla et al, 2012):

(a) The drugs should have high solubility and high permeability according to BCS. However, other classification systems are part of current investigations.

(b) 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 and Buffer pH 6.8 or simulated intestinal fluid (SIF) without enzymes, all in 900 ml and at 37°C.

(c) Twelve's samples in each media, paddle rotating at 50 rpm or basket at 100 rpm.

(d) Sampling times are 10, 15, 20, 30, 45 and 60 minutes.

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

(f) The products are similar if the similarity factor $f_2 \geq 50$ and both products show $\geq 85\%$ dissolution in 15 min.

Following equation is used to calculate f_2 :

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

Where, T_t and R_t are percent drug dissolved at each time point for test and reference product, respectively.

Different guidance to IR oral dosage form for biowaiver

FDA (WHO, 2005):

a. Should contain a BCS I APIs.

- b. Dissolution requirement should release at least 85% of its content in 30 minutes in three different buffers (pH1.2 or simulated gastric fluid, pH4.5 and pH6.8 or simulated intestinal fluid) in a paddle (50 rpm) or basket (100 rpm.) apparatus at 37°C and a volume of 900 ml.
- c. Should not contain excipients which could influence the absorption of the drug.
- d. Should not contain a drug with a narrow therapeutic index.
- e. Should not be designed to be absorbed from the oral cavity.
- f. If all these conditions are met dissolution similarity between test and reference drug product in the three media based on the criteria that $f_2 \geq 50$ are sufficient to qualify the test drug product for a biowaiver should both the test and reference product show > 85 % dissolution within 15 minutes in each of the three media, then the test product qualifies for a biowaiver without the need to apply the f_2 criteria for similar of the dissolution profiles.

WHO (WHO, 2006):

- a. Should contain APIs of BCS I and certain APIs of BCS II, BCS III (Table 2).
- b. For APIs of BCS I greater than 85% dissolution of the labeled amount is required within 30min in standard media at pH 1.2, 4.5 and 6.8 using the paddle apparatus at 75rpm or alternatively the basket apparatus at 100rpm. The dissolution profiles of the comparator and the multisource products should be compared by an $f_2 > 50$ or an equivalent statistical criterion. If after 15 min more than 85% are released from the comparator and the multisource formulation under the above-mentioned conditions the product will be considered very rapidly dissolving. In this case, the products are deemed to be equivalent and a profile comparison is not required.
- c. For APIs belonging to BCS II, is rapidly dissolving i.e. 85% or more dissolution of the labeled amount of the APIs should be achieved within 30 min in standard media at pH 6.8 using the paddle apparatus at 75 rpm or alternatively the basket apparatus at 100rpm, and the multisource product exhibits similar dissolution profiles, as determined with the f_2 value or equivalent statistical evaluation, to those of the comparator product in buffers at all three pH values (pH 1.2, 4.5 and 6.8).

d. APIs belonging to BCS III to be considered for a biowaiver, if both the multisource and the comparator product are very rapidly dissolving; 85% or more dissolution of the labeled amount of the APIs should be achieved within 15min in standard media at pH 1.2, 4.5 and 6.8 using the paddle apparatus at 75 rpm or alternatively the basket apparatus at 100 rpm.

e. Should contain excipients which have been used in a similar amount in other formulation of the same.

f. Risk of an incorrect biowaiver outweighed by biowaiver process.

Table 2: Medicines included in the WHO list of essential medicines for which biowaiver is possible (WHO, 2006; Thapa, 2010).

Abacavir; acetylsalicylic acid; acyclovir; allopurinol; amiloride hydrochloride; amitriptyline HCl; amlodipine; amodiaquine(base); amoxicillin+clavulanic acid; amoxicillin anhydrous; ascorbic acid; atenolol; beznidazole; biperiden HCl; calcium folinate; chloramphenicol; chloroquine phosphate or sulfate; chlorambucil; chloramphenamine hydrogen; maleate; ciprofloxacin HCl; clindamycin; clomifen citrate; clomipramine hydrochloride; cloxacillin (as sodium salt); codeine phosphate; cyclophosphamide; cycloserine; diazepam; didanosine; diethylcarbamazepine dihydrogen citrate; digoxin; doxycycline HCl; enalapril; ergocalciferol; ethambutol HCl; ethionamide; ethylestradiol; ethylestradiol+levonorgesterol; ethylestradiol+norethiesterone; ethosuximide; ferrous salt; ferrous salt+folic acid; fluconazole, flucytosine; folic acid, furosemide; hydralazine HCl; hydrochlorothiazide; ibuprofen; isoniazide; levamisole hydrochloride; levodopa+carbidopa; levofloxacin; levonorgestrel; levothroxine sodium salt; lithium carbonate; DL- methionine; metformin HCl; methyl dopa; methotrexate sodium salt, metoclopramide HCl; metronidazole; morphine sulfate; neostigmine bromide; nicotinamide; nifurtimox; norethisterone; ofloxacin; paracetamol; penicillamine; phenobarbital; phenoxymethyl penicillin (as potassium salt); paentamine; phenytoin sodium salt; potassium iodide; prednisolone; primaquine diphosphate; procabazine HCl; proguanil HCl; promethazine HCl, propranol HCl; propylthiouracil; pyrazinamide; pyridoxine HCl; pyridostigmine bromide; quinine bisulfate or sulfate; ranitidine HCl; riboflavin; salbutamol sulfate; stavudine; tamoxifen citrate; thiamine HCl; warfarin sodium salt; zidovudine; zinc sulfate.

EUMA (EMA, 2008)

- a. BCS based biowaiver are intended only to address the question of bioequivalence between a test and reference product. BCS I and BCS III APIs are suitable for biowaiver.
- b. The BCS I APIs should release > 85 within 15 minutes in three different media –pH1.2 (0.1 N HCl or SGF without enzymes), pH4.5 and pH6.8 or SIF without enzymes.
- c. The BCS III APIs should release > 85 within 15 minutes in three different media –pH1.2 (0.1 N HCl or SGF without enzymes), pH4.5 and pH6.8 or SIF without enzymes. And excipients qualitatively the same and quantitatively very similar.

CONCLUSION

In-vitro under biowaiver studies help to replace expensive *in-vivo* testing with a simpler, more easily implemented, routinely monitored and more reliable *in-vitro* dissolution test would ensure clinical performance. And it eases to pharmaceutical manufacturers of both new medicines and generic drug products to avoid unnecessary human experiments and to avoid any time of the product development. And it can be seen that the FDA guidance on biowaiver is strict than WHO and YU LX et al concluded on extension potential for biowaiver.



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