الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guidelines for Biowaiver

Based on Biopharmaceutics Classification System (BCS) For Immediate-Release (IR) Solid Oral Dosage Forms

Version 2.0

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Saudi Food & Drug Authority

Drug Sector

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

Version	Author	Date	Comments
1.0	Executive directorate of Product Evaluation and Standards setting	17 September 2012	Draft
1.1	Executive directorate of Product Evaluation and Standards setting	15 July 2013	Final & update
2.0	Executive Directorate Of Benefits And Risks Evaluation	05 January 2022	Update (Next page shows the updated details

What is New in version no. 2.0?

The following table shows the update to the previous version:

Section	Description of change
3.1 Solubility	**<u>Update</u>** A drug substance is considered highly soluble when the highest single dose (in mg) is soluble in 250 ml or less of aqueous media over the pH range of 1.2-6.8.

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1. INTRODUCTION:

This guidance is provided by Saudi Food and Drug Authority (SFDA) in order to provide a recommendation for the applicant to answer their concerns. These guidelines are intended to facilitate and support the workflow of drug registration.

It is important to note that the SFDA reserves the right to request any additional information and data not specifically described in this document, in order to assess adequately the safety, efficacy and quality of drug products. The SFDA is committed to ensuring that such requests are justifiable and decisions are clearly documented.

The information presented in this guidance is based on recommendations of the:

- The GCC guidelines for bioequivalence, version 2, 2011.

- FDA, Centre for Drug Evaluation Evaluation and Research (2000), as described in the "Waiver of in vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System";

- WHO, as described in the "Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms Annex 8".

- EMA, as described in the "Guideline on the investigation of bioequivalence (2010)" ; and

- The International Pharmaceutical Federation (FIP).

2. BACKGROUND:

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is meant to reduce in-vivo bioequivalence studies, i.e., it may represent a surrogate for in-vivo bioequivalence. In-vivo bioequivalence studies may be exempted if an assumption of equivalence in-vivo performance can be justified by satisfactory in-vitro data.

Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index.

The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form. However, it is not applicable for sublingual, buccal, and modified release formulations. For orodispersible formulations the BCS-based biowaiver approach may only be applicable when absorption in the oral cavity can be excluded.

BCS-based biowaivers are intended to address the question of bioequivalence between specific test and reference products. The principles may be used to establish bioequivalence in applications for generic medicinal products, extensions of innovator products, variations that require bioequivalence testing and between early clinical trial products and to be marketed products.

3. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM:

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows:

Class 1: High Solubility- High Permeability

Class 2: Low Solubility- High Permeability

Class 3: High Solubility- Low Permeability

Class 4: Low Solubility- Low Permeability

Biowaiver may be applicable when the active substance(s) in test and reference products are identical and belong to BCS-Class I on Biowaiver monographs published by International Pharmaceutical Federation (FIP) or in FDA website under " Bioequivalence recommendations for specific product". These sources provide detailed information which should be taken into account whenever available in the Biowaiver consideration.

Biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance from that of the reference

product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept.

The recommended methods for determining solubility, permeability, and in-vitro dissolution are discussed below.

3.1 Solubility:

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. A drug substance is considered highly soluble when the highest single dose (in mg) is soluble in 250 ml or less of aqueous media over the pH range of 1.2-6.8. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

3.2 Permeability:

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic bioavailability) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, non-human systems capable of predicting the extent of drug absorption in humans can be used (e.g., in-vitro epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 85% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

3.3 Dissolution:

In this guidance, an IR drug product is considered rapidly dissolving when not less than 85% of the labeled amount of the drug substance dissolves within 30 minutes. A brief description of the IR products used for dissolution testing, including information on batch (number, type and size), expiry date and strength. 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.

Data supporting similarity in dissolution profiles between the test and reference products in each of the three media, using the similarity factor (f2) should be provided. For more information on Similarity of dissolution, please refer to The GCC guidelines for bioequivalence.

3.4 Additional Considerations For Requesting a Biowaiver:

When requesting a BCS-based waiver for in-vivo BA/BE studies for IR solid oral dosage forms, applicants should note that the following factors can affect their request or the documentation of their request.

3.5 Excipients:

Although the impact of excipients in IR dosage forms on bioavailability of highly soluble and completely absorbable drug substances (i.e., BCS-Class I) is considered rather unlikely but it cannot be completely excluded. Therefore, even in the case of Class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the reference product.

As a general rule, for BCS-Class I drug substances well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be considered and discussed. A description of the function of the excipients is required with a justification whether the amount of each excipient is within the normal range. Acceptable excipients to SFDA can be found in the FDA website under “Inactive Ingredient for Approved Drug Products”.

The use of excipients that might affect bioavailability must be avoided unless they have been used in the reference product in the same qualitative and quantitative manner.

Such excipients include those with possible impact on:

- gastrointestinal motility.
- susceptibility of interactions with the drug substance (e.g. complexation).
- drug permeability.
- interaction with membrane transporters.

Exceptions:

BCS-based biowaivers are not applicable for the following:

A. Narrow Therapeutic index:

This guidance defines narrow therapeutic range drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, applicant should contact the appropriate review division to determine whether a drug should be considered to have a narrow therapeutic range.

B. Products Designed to be Absorbed in the Oral Cavity:

A request for a waiver of in-vivo BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets).

4. SFDA APPLICATIONS OF THE BCS:

A. New Chemical Entity (NCE):

Once the in-vivo bioavailability of a formulation is established during the NCE registration period, waivers of subsequent in-vivo bioequivalence studies, following major changes in components, composition, and/or method of manufacture (variation(s)) may be possible using the BCS. BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, and/or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar in-vitro dissolution profiles. This approach is useful only when the drug substance is highly soluble and highly permeable (BCS Class 1), and the formulations pre- and post-change are pharmaceutical equivalents. BCS-based biowaivers are intended only for bioequivalence studies. They do not apply to food effect bioavailability studies or other pharmacokinetic studies.

B. Generics:

BCS-based biowaivers can be requested for rapidly dissolving IR test products containing highly soluble and highly permeable drug substances (BCS Class 1), provided that the reference drug product is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference drug product. This approach is useful when the test and reference dosage forms are pharmaceutical equivalents.

C. Post-approval Changes (Variations):

BCS-based biowaivers can be requested for significant post approval changes (variations in components and composition) to a rapidly dissolving IR product containing a highly soluble, highly permeable drug substance (BCS Class 1), provided that dissolution remains rapid for the post change product and both pre- and post-change products exhibit similar dissolution profiles. This approach is useful only when the drug products pre- and post-change are pharmaceutical equivalents.

5. BIOWAIVER APPLICATION TO SFDA:

For a product to be applied to SFDA for a Biowaiver, it must belong to BCS Class 1 drug list (section 3). The application should include all the dissolution studies according to (section 3.3) and the required information on the excipients (section 3.5).

REFERENCES:

1. The GCC guidelines for bioequivalence, version 2, 2011.

2. Guidance for Industry: "Waiver of in vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System". U.S. Food and Drug Administration, Center for Drug Evaluation and Research, 2000.

3. WHO, Annex 8, Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms.

4. EMA as described in "Guideline on the investigation of bioequivalence", 2010.

5. The International Pharmaceutical Federation (FIP).

ACRONYMS

SFDA Saudi Food and Drug Authority.

GCC The Cooperation Council For The Arab States of The Gulf.

EMA European Medicines Agency.

FIP The International Pharmaceutical Federation.

BCS Biopharmaceutics Classification System.

IR Immediate-Release.

BE Bioequivalence.

BA Bioavailability.

f2 Similarity factor.

NCE New Chemical Entity.