

General Notes on Biopharmaceutics Classification System (BCS)-based Biowaiver Applications

In the WHO Prequalification Team: medicines (PQTm), biowaivers based on the Biopharmaceutics Classification System (BCS) are intended only to investigate bioequivalence and do not apply to other bioavailability or pharmacokinetic studies.

1. BACKGROUND

The information presented in this guidance is based on:

- a) WHO "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability". Technical Report Series 937, Annex 7, 2015
- b) US FDA "Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, 2000", available at: <http://www.fda.gov/OHRMS/DOCKETS/98fr/3657gd3.pdf>
- c) European Medicines Agency (EMA) "Guideline on the Investigation of Bioequivalence", 2010, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

In principle, highly soluble active pharmaceutical ingredients (APIs) with known human absorption/permeability characteristics have been identified as eligible for the BCS-based biowaiver approach for establishing the safety and efficacy of a multisource finished pharmaceutical product (FPP). Therefore, both BCS Class I (high solubility and high permeability) and Class III (high solubility and low permeability) APIs are considered to be eligible in cases where sufficient information concerning the API is available to complete an accurate risk-based assessment for the use of this approach.

In order to maximize opportunities to use BCS-based biowaivers, PQTm has established a two-pronged approach for biowaiver applications as follows: (1) for products containing APIs for which PQTm has assigned a BCS classification (see below), a BCS-based biowaiver application can be made without providing data for classification of the API; and (2) for products containing APIs not included in the table below, a BCS-based biowaiver application can be submitted if it contains the solubility and absorption/permeability data necessary to properly classify the API(s) as either BCS Class I or III.

Option 1: Eligible APIs assigned a BCS classification by PQTm

Based on the scientific principles outlined in the guidelines listed above, PQTm has reviewed the available data related to the solubility, absorption, and dissolution characteristics of the medicinal products invited for PQTm evaluation, and has identified the following APIs to be eligible for BCS-based biowaiver applications:

Active pharmaceutical ingredient (API)	Therapeutic group	Highest oral dose [mg]	BCS Class
Abacavir (as sulfate)	Antiretroviral	600	III
Emtricitabine	Antiretroviral	200	I
Lamivudine	Antiretroviral	300	III
Stavudine	Antiretroviral	40	I
Zidovudine	Antiretroviral	300	I
Linezolid	Antibacterial	600	I
Fluconazole* (Polymorphs II & III)	Antifungal	800	I
Ethambutol	Anti-tuberculosis	400	III
Isoniazid	Anti-tuberculosis	300	III
Levofloxacin	Anti-tuberculosis	750	I
Moxifloxacin (as hydrochloride)	Anti-tuberculosis	400	I
Ofloxacin	Anti-tuberculosis	400	I
Pyrazinamide	Anti-tuberculosis	500	III
Diethylcarbamazine	Anti-parasitic	500	III**

* - Fluconazole polymorph I does not fulfill the requirements for BCS high solubility.

** - Insufficient information was available to determine the absorption/permeability classification of diethylcarbamazine (DEC), therefore DEC has been assigned the provisional classification of Class III. If adequate absorption/permeability data can be provided in an application, as described below, finalization of the classification as either Class I or III can be undertaken.

Option 2: Full biowaiver application for APIs not assigned to a BCS class by PQTm

PQTm invites interested manufacturers to submit the data necessary to accurately classify an API(s) as a part of a BCS-based biowaiver application for a FPP containing that API(s). As above, to be eligible for a BCS-based biowaiver, it must be established that the API is a BCS Class I or III drug substance.

BCS-based biowaiver applications for this option must include complete API solubility and absorption information consistent with the requirements described in Section III of Annex III of the EMA *Guideline on the Investigation of Bioequivalence* (2010).¹ These data and information should be summarized in the appropriate sections of the *Biowaiver Application Form: Biopharmaceutics Classification System (BCS)* with appropriate references to the detailed data provided in annexes to the application form.

¹ Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

2. GENERAL REQUIREMENTS

BCS-based biowaivers are applicable for immediate-release solid oral dosage formulations containing one or more of the API(s) mentioned above if the required data ensure the similarity of the submitted pharmaceutical product and the appropriate pharmaceutically equivalent comparator product. Until further notice, *in vivo* bioequivalence studies are required for invited monocomponent and fixed-dose combination products containing other APIs.

Comparator products used in BCS-biowaiver applications should be selected from the current list of PQTm recommended comparator products, including the appropriate fixed-dose combination product.

Biowaiver-based dossiers should contain relevant information and data as outlined in the following paragraphs:

3. COMPARATOR PRODUCT SUITABILITY

Identification by PQTm of an API to be eligible for a BCS-based biowaiver application is made purely on the solubility, absorption, safety and related properties of the API (Class I or Class III). It does not imply that the recommended comparator product(s) will be rapidly dissolving in the case of Class I APIs or very rapidly dissolving in the case of Class III APIs, which is a requirement for BCS-based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the PQTm website is indeed suitable for a BCS based-biowaiver application before product development.

Note that rapidly dissolving, or very rapidly dissolving, properties of a product are not required for *in vivo* bioequivalence studies. Thus, though a listed comparator product may not be suitable for BCS-based biowaiver purposes, it is still suitable for *in vivo* bioequivalence studies.

4. FINISHED PHARMACEUTICAL PRODUCT (FPP) CRITERIA

4.1 “Biobatch” selection

As with all FPP applications, the consistency of the manufacturing method and the quality of the test product must be demonstrated in the relevant sections of the quality part of the dossier.

It is recommended that samples of the test product be taken from batches of industrial scale. However, when this is not possible, a batch of 1/10 or larger of the expected full production batch, or 100 000 units, whichever is greater, can also be used as the test product, provided these batches are the same as the production batches in manufacturing method, quality and composition.

The API content or potency of the comparator product should be close to the label claim, and the difference in API content or potency between the test and comparator products should be not more than 5%.

4.2 Excipients

BCS Class 1 APIs

In order to minimize the possible impact of excipients on the bioavailability of the API, it is a significant asset to a biowaiver application if the proposed (test) product contains similar amounts of the same excipients as the comparator product. Information related to this issue is usually available from public sources of stringent regulatory authorities (SRAs). At a minimum, well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be discussed. Excipients that may affect the bioavailability of the API (e.g. mannitol, sorbitol, surfactants) should be used with care, and if present, should not differ qualitatively and quantitatively between the proposed product and the comparator product.

BCS Class 3 APIs

For BCS Class 3 APIs, excipients in the proposed product formulation must be qualitatively the same and quantitatively very similar to that of the comparator product, except excipients that may affect the bioavailability of the API (e.g., mannitol, sorbitol, surfactants) which should not differ qualitatively or quantitatively between the proposed product and the comparator product. The term 'very similar' is defined as per 'Level 1 Changes' according to the SUPAC (Scale-Up and Postapproval Changes, US FDA) guidance.²

In addition, with respect to isoniazid-containing products, lactose and/or other 'reducing sugars' should not be included in the formulation of the proposed product unless present in the same amount in the comparator product.³

5. COMPARATIVE IN-VITRO DISSOLUTION

Dissolution tests should be performed using more than one batch (12 tablets per batch for each study) of the appropriate comparator product, if possible, using the mean data of these batches for profile comparison. The "mean data" is the average of the individual batch data of the comparator batches for each pH medium studied i.e. one set of data and one profile is derived from the multiple batches for each medium and compared against the test biowaiver batch data and profile. Compilation of 'historical' data is not acceptable.

Comparative in vitro dissolution should ensure the similarity of the test and comparator product in three different pH media considered relevant for absorption in the gastrointestinal tract. Discussion and/or interpretation of relevant differences between dissolution profiles as to their in vivo relevance is considered inappropriate since, in the framework of BCS-based biowaivers, respective investigations do not represent any in vitro/in vivo correlation.

Comparative in vitro dissolution should be performed with 12 units of actual batches in 900 ml or less of standard buffer media at pH 1.2, 4.5 and 6.8, at 37°C ± 0.5°C, using the paddle apparatus at 75 rpm or less, or the basket apparatus at 100 rpm. Surfactants should not be used. Samples should be filtered immediately to prevent continuation of dissolution. The filters can be in-line or at the end of the sampling probe or both. The sampling intervals should be short for a scientifically sound comparison of the profiles (e.g. 5, 10, 15, 20, 30 and 45 minutes). Inclusion of the 15-minute time point in the protocol is of strategic importance for profile similarity determinations.

The following definitions will apply:

- "very rapidly" dissolving products: at least 85 % of the labelled amount is released within 15 minutes or less from the test and the comparator product. In this case profile comparison is not needed.
- "rapidly" dissolving products: at least 85 % of the labelled amount is released within 30 minutes or less from the test and the comparator product; profile comparisons using e.g. f2 testing, are required.

The experimental setting should be qualified according to current standards, and analytical methods should be fully validated and comprehensively described. Regarding validation acceptance criteria and method details for dissolution assays, clear and traceable cross-referencing to the quality part of the dossier is acceptable.

² *Guidance for Industry: Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070636.pdf

³ Becker et al. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Isoniazid. *Journal of Pharmaceutical Science*, 96 (2007) 522.

BCS Class I APIs

For BCS Class I APIs, the test and comparator products must display either very rapid or similarly rapid *in vitro* dissolution characteristics under the defined conditions in order to be eligible for a biowaiver.

BCS Class III APIs

For BCS Class III APIs, the test and comparator products must display very rapid *in vitro* dissolution characteristics under the defined conditions in order to be eligible for a biowaiver.

For further guidance on biowaiver dissolution conditions and requirements and for determination of similarity of dissolution profiles, please consult:

WHO "[Multisource \(generic\) pharmaceutical products: guidelines on registration requirements to establish interchangeability](#). Technical Report Series 937, Annex 7, 2015

5.1 Format of *in vitro* dissolution study report

The report on a dissolution study used in the biowaiver application should include a study protocol and at least the following information:

1. Purpose of study
2. Products / batch information
 - a. Batch numbers, manufacturing and expiry dates, batch size of the test product, Certificates of Analysis (CoAs) and packaging of the batches used in the study
 - b. Batch manufacturing record(s) for the batch of the test product used in the comparative dissolution study.
3. Full dissolution conditions and method, as well as the number of units (tablets, capsules, etc) per study. It should be indicated how and when the samples were filtered. Any problems with pH-related stability of samples should be indicated and discussed in terms of preventive handling measures, analysis and interpretation of data.
4. Analytical method including validation, or reference to the quality part of the dossier.
5. Results (% API dissolved)
 - a. Tabulated (individual results, mean and %CV)
 - b. Graphically
 - c. Similarity determination / f2 calculation if necessary and applicable
6. Conclusion/recommendation.

6. DOCUMENTATION REQUIRED FOR SUBMISSION

The Biowaiver Application Form: Biopharmaceutics Classification System (BCS) must be completed and submitted in MS Word format. The instructions for completion of the biowaiver application form are provided at the top of the form. All supporting documentation including comparator product information, Certificates of Analysis, and the comparative dissolution study report should be provided as annexes to the application form.