Biopharmaceutics Classification System (BCS)-based biowaiver applications: anti-tuberculosis medicines

This guidance is additional to principles described in the "*General notes on biowaiver applications*" and the information presented in this guidance is based on the recommendations of the WHO, as described in the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability". In: *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization. WHO Technical Report Series, No. 937, 2006, Annex 7.

WHO Prequalification of Medicines Programme (PQP) has reviewed the existing evidence on the bioavailability and dissolution data of the medicines invited to the PQP evaluation, and has identified the following anti-tuberculosis medicines to be eligible for BCS-based biowaiver applications for mono-component products:

- Ethambutol
- Isoniazid
- Levofloxacin
- Ofloxacin
- Pyrazinamide

Until further notice, *in vivo* bioequivalence studies are required for invited monocomponent and fixed-dose combination products containing other active pharmaceutical ingredients (APIs) of anti-tuberculosis medicines.

Biowaiver status of selected anti-tuberculosis APIs

For the WHO-PQP, the below-noted anti-tuberculosis APIs have been assigned BCS classifications as follows:

Drug substance	*Highest oral dose strength [mg]*	*BCS Class*	*BCS-based biowaiver*
Ethambutol	400	3	yes*[1]
Isoniazid	300	3/1	yes*[2]
Levofloxacin	500	1	yes
Ofloxacin	400	1	yes
Pyrazinamide	400	3/1	yes*[3]
Rifampicin	300	2	no**

[1] Becker C, Dressman J, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM: Biowaiver monographs for immediate release solid oral dosage forms: ethambutol dihydrochloride. J Pharm Sci 2007 Aug 21 [Epub ahead of print].

[2] Becker C, Dressman J, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM: Biowaiver monographs for immediate release solid oral dosage forms: isoniazid. J Pharm Sci 96 (2007) 522.

[3] Becker C, Dressman J, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM: Biowaiver monographs for immediate release solid oral dosage forms: pyrazinamde. J Pharm Sci 2008 Feb 12 [Epub ahead of print].

* ***Ethambutol, isoniazid and pyrazinamide*** are classified as being borderline BCS Class 3/1 drugs, *i.e.* the drug compounds are highly soluble but absorption is limited due to various reasons. Therefore a BCS-based biowaiver is possible for these APIs only if the following requirements are fulfilled:

- The test product contains qualitatively the same excipients as the comparator product
- The test product formulation is quantitatively very similar to that of 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. In addition, particular recommendations should be considered for isoniazid products *i.e.,* lactose and/or other 'reducing sugars' should not be contained in the formulation unless in the same amount as in the comparator product[4].
- The *in vitro* dissolution reaches at least 85 % within 15 min for both the test and the comparator products. A longer time to achieve at least 85% dissolution (not exceeding 30 minutes) is acceptable if the dissolution profiles are similar and the product composition (test and comparator) is very similar.

** No BCS-based biowaivers will be considered for ***rifampicin*** containing products since the drug substance is a BCS Class 2 drug and, in addition, has certain problematic physicochemical properties.

Comparator product suitability

Identification by WHO of an API to be eligible for a BCS-based biowaiver application is made purely on the solubility, permeability, safety and related properties of the API (Class 1 or Class 3). It does not imply that the recommended comparator product(s) will be rapidly dissolving in case of Class 1 APIs (or very rapidly dissolving in case of Class 3 API), which is a requirement for BCS based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the Prequalification 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] Becker et al. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: isoniazid. J Pharm Sci 96 (2007) 522

General notes on Biopharmaceutics Classification System (BCS)-based biowaiver applications

In the WHO Prequalification of Medicines Programme, 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 recommendations of the:

a) WHO, as described in the "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability". In: *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization. WHO Technical Report Series, No. 937, 2006, Annex 7 available at http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS04_093Rev4_final.pdf

b) US-FDA, as described in "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/cder/Guidance/3618fnl.pdf

c) EMA, as described in "Guideline on the Investigation of Bioequivalence", 2010, available at: http://www.ema.europa.eu/pdfs/human/qwp/140198enrev1fin.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).Th erefore, both BCS Class I (high solubility and high permeability) and Class III (high solubility and low permeability) APIs, where sufficient information concerning the API is available to complete an accurate risk-based assessment for the use of this approach, are considered to be eligible.

Based on the scientific principles outlined in the guidelines listed above, the WHO Prequalification of Medicines Programme (PQP) has reviewed the available data related to the solubility, absorption, and dissolution characteristics of the medicinal products invited to the PQP 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	3
Emtricitabine	Antiretroviral	200	1
Lamivudine	Antiretroviral	300	3

Stavudine	Antiretroviral	40	1
Zidovudine	Antiretroviral	300	1
Ethambutol	Anti-tuberculosis	400	3
Isoniazid	Anti-tuberculosis	300	3
Levofloxacin	Anti-tuberculosis	750	1
Moxifloxacin (as hydrochloride)	Anti-tuberculosis	400	1
Ofloxacin	Anti-tuberculosis	400	1
Pyrazinamide	Anti-tuberculosis	500	3

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 WHO PQP 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 WHO 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 1 or Class 3). It does not imply that the recommended comparator product(s) will be rapidly dissolving in the case of Class 1 APIs or very rapidly dissolving in the case of Class 3 API, which is a requirement for BCS-based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the Prequalification 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.Fi nished 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 considered to be 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[1].

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.[2]

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.

---

1 *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

2 Becker et al. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Isoniazid. J Pharm Sci 96 (2007) 522.

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.

BCS Class 1 APIs
For BCS Class 1 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 3 APIs
For BCS Class 3 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:
Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*. Geneva, World Health Organization. WHO Technical Report Series, No. 937, 2006, Annex 7.

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
   - 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
   - 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)
   - Tabulated (individual results, mean and %CV)
   - Graphically
   - 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.