



BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS - M9

Step 2 document – to be released for comments

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International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use



ICH M9: BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS

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Background

- This document has been signed off as **Step 2** document (7 June 2018) to be issued by the ICH Regulatory Members for public consultation
- This document was developed based on a Concept Paper (7 October 2016) and a Business Plan (7 October 2016)
- Anticipating finalization as **Step 4** document to be implemented in the local regional regulatory system: 05 / 2019

Key Principles

- This proposed new multidisciplinary Guideline will address Biopharmaceutics Classification System (BCS)-based waivers of bioequivalence studies (biowaivers).
- This Guideline will provide recommendations on how to determine the biopharmaceutics classification of drug substances.
- In addition, the Guideline will provide recommendations to support the waiver of bioequivalence studies.

Key Principles (continued)

- **The BCS-based biowaiver is only applicable to immediate release, solid orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation.**
- **Drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver.**
- **Fixed-dose combination products are considered eligible for a BCS-based biowaiver in cases where all the active drug substances fulfill the criteria.**

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Guideline Objectives

- **The BCS-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies.**
- **This guidance will provide recommendations to support the biopharmaceutics classification of drug substances and the BCS-based biowaiver of bioequivalence studies for drug products.**
- **This Guideline will result in the harmonisation of current regional guidelines/guidance, reduce the need for in vivo bioequivalence studies and support streamlined global drug development.**

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Table of Guideline Contents

- **1. Introduction**
 - 1.1. Background and Objective
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- **2. Biopharmaceutics classification of the drug substance**
 - 2.1. Solubility
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- **3. Support of the eligibility of a drug product for a BCS-based biowaiver**
 - 3.1. Excipients
 - 3.2. In vitro dissolution
- **4. Documentation**
- **5. Glossary**

Summary of Guideline Content

- **The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance, resulting in 4 classes:**
 - Class I: high solubility, high permeability
 - Class II: low solubility, high permeability
 - Class III: high solubility, low permeability
 - Class IV: low solubility, low permeability

Summary of Guideline Content (continued)

- A drug substance is considered highly soluble if the highest single therapeutic dose or highest strength (if justified) is completely soluble in 250 ml or less of aqueous media over the pH range of 1.2 – 6.8 at 37°C and at pKa if within this pH range.
- The lowest measured solubility over the pH range 1.2-6.8 is used to classify the drug substance solubility.
- Consideration should be given to experimental conditions (see next slide).

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Summary of Guideline Content (continued)

- **Experimental conditions to take into account, e.g.**
 - use of shake-flask technique or an alternative method
 - testing pH at beginning and at end of the experiment; the pH should be adjusted, if necessary
 - at least 3 replicate determinations at each pH level, using a validated method
 - the drug substance should be stable in all media

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Summary of Guideline Content (continued)

- **A drug substance is considered highly permeable if $\geq 85\%$ of the administered dose is absorbed.**
- **Supported by e.g.**
 - the absolute bioavailability is $\geq 85\%$
 - $\geq 85\%$ of the administered dose is recovered in urine and/or feces as absorbed drug material
 - validated and standardized in vitro methods using Caco-2 cells
 - to be considered:
 - stability of the drug substance in the gastrointestinal tract
 - human in vivo data from published literature may be acceptable

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Summary of Guideline Content (continued)

- **A drug product is eligible for a BCS-based biowaiver provided that:**
 - the drug substance is a Class I or Class III drug
 - the drug product is an immediate-release oral dosage form with systemic action
 - the drug product is a dosage form that is pharmaceutically equivalent to the reference product
 - criteria with respect to composition (excipients) and in vitro dissolution performance of the drug product should be fulfilled

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Summary of Guideline Content (continued)

- **Composition of drug product:**
 - excipient differences between the proposed test and the reference product should be assessed for their potential to affect in vivo absorption
 - for BCS Class I drugs, qualitative and quantitative differences in excipients are permitted, except for excipients that may affect absorption, which should be qualitatively the same and quantitatively similar, i.e., within $\pm 10.0\%$ of the amount of that excipient in the reference product
 - for BCS Class III drugs, all of the excipients should be qualitatively the same and quantitatively similar
- note: a table with allowable differences in excipients is included in the guideline

Summary of Guideline Content (continued)

- **In vitro dissolution:**
 - comparative in vitro dissolution experiments should use compendial apparatuses and validated analytical methods
 - the following conditions should be taken into account:
 - paddle (50 rpm) or basket (100 rpm)
 - 900 ml or less media (37°C)
 - pharmacopoeial buffers at at least pH 1.2, 4.5 and 6.8
 - use of organic solvent or surfactants are not allowed
 - apply filtration of samples
 - the use of specific enzymes may be acceptable (gelatin cross-linking)
- note: purified water may be used as a dissolution medium in some regions

Summary of Guideline Content (continued)

- **In vitro dissolution (continued):**
 - Class I: both the test product and reference product should display either very rapid (≥ 85 for the mean percent dissolved in ≤ 15 minutes) or rapid (≥ 85 for the mean percent dissolved in ≤ 30 minutes) and similar in vitro dissolution (similarity factor f_2) in all media (at all pHs tested)
 - Class III: both the test product and reference product should display very rapid (≥ 85 for the mean percent dissolved in ≤ 15 minutes) in vitro dissolution in all media (at all pHs tested)

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Considerations

- **All study protocols including standards, quality assurance and testing methods should be appropriately detailed and validated according to current regulatory guidance's and policies.**
- **Complete data should be included in module 5.3.1.2., eventually with cross references to Module 3, if applicable, and Module 5.4 (literature references).**

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Conclusions

- **This harmonised guidance on the basic requirements for accepting and applying BCS-based biowaivers, reduces the need for carrying out additional clinical (bioequivalence) studies in humans. This may accelerate development and drug approval and may lower the costs significantly.**

Contact

- **For any questions please contact the ICH Secretariat:**

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