Final endorsed Concept Paper
M9: Biopharmaceutics Classification System-based Biowaivers
7 October 2016

Type of Harmonisation Action Proposed

This proposed new multidisciplinary guideline will address Biopharmaceutics Classification System (BCS)-based biowaivers. This guideline will provide recommendations to support the biopharmaceutics classification of medicinal products and will provide recommendations to support the waiver of bioequivalence studies.

This will result in the harmonisation of current regional guidelines/guidance and support streamlined global drug development.

Statement of the Perceived Problem:

Biopharmaceutics Classification System (BCS)-based biowaivers may be applicable to BCS Class I and III drugs, however BCS-based biowaivers for these two classes are not recognized worldwide. Regulatory guidelines/draft guidance which includes the possibility of BCS-based biowaivers have been issued in, for instance, the EU, US, Canada and within the WHO. Also, Japanese guideline includes the possibility of biowaivers based on the extent of formulation change. However, it appears from these guidelines that BCS based biowaivers may not be recognized globally or that the requested supportive data for such applications differs. In addition, even the classification itself may differ. This means that pharmaceutical companies have to follow different approaches in the different regions.

Current bioequivalence/biowaiver guidelines/guidances include:

EU	Guideline on the investigation of bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1, 2010)
US	Waiver of *In Vivo* Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry (draft 2015)
Japan	Guideline for Bioequivalence Studies of Generic Products (2012)
Canada	Guidance Document: Biopharmaceutics Classification System Based Biowaiver (2014)
WHO	WHO Technical Report Series 992. WHO Expert Committee on Specifications for Pharmaceutical Preparations, 49th report, Annex 7.

Issues to be Resolved:

The main issues to be resolved can be divided into supportive data for the classification of the medicinal products into one of the 4 classes of BCS and supportive data for the waiver itself. The guidance/recommendations in the guideline will address the following issues:

1. Supportive data for classification

- **Solubility**: Considering a drug highly soluble or low soluble, the highest therapeutic dose as mentioned in the product label for the specific medicinal product can be taken into account or the highest dose strength of the medicinal product
- **Permeability**: Different methods exist to estimate permeability. Harmonisation is sought on whether the estimation of permeability should be based upon *in vitro* data, *in vivo* data or both. Furthermore, when identified the most suitable method, cut-off values should be established to consider a medicinal product highly permeable or low permeable.
- Are literature data acceptable to support the BCS classification?

2. Supportive data for a waiver

- Establish cut-off values of dissolution criteria depending on whether the drug is considered a BCS Class I or a BCS Class III drug (note: depending on the applicability/acceptability of a BCS waiver for Class I and III drugs).
- With regard to comparability of the Test or proposed formulation versus the Reference formulation or Comparator formulation, establishing what are critical excipients which may influence the rate and/or extent of absorption of a drug. Additionally, criteria to consider formulations quantitatively comparable may be established, and the type of data needed to demonstrate that an excipient is non-critical may be clarified.

Additionally, the following issues will be resolved if possible:

- As *in vitro* dissolution testing is required for a BCS-based biowaiver, the conditions for dissolution testing should be established. Can different criteria be applied than the default conditions, e.g. a higher or lower agitation speed? If so, what kind of justification could be considered acceptable?
- Clarify if a BCS based biowaiver is only applicable for pharmaceutical equivalents. Furthermore, in case the Reference formulation or Comparator formulation is marketed with more than 1 strength, for example 10 and 20 mg IR release tablets, clarify whether the BCS based biowaiver should be matched 1 to 1, i.e., comparability should be shown between the 10 mg of the Reference/Comparator and 10 mg Test formulation and between the 20 mg of the Reference/Comparator and 20 mg Test formulation. Or is a full BCS based biowaiver sufficient for 1 strength and the other strength can be accepted based upon a biowaiver for additional strength.

Background to the Proposal:

Although the scientific data that can be used to support BCS-based biowaivers is the same, it seems that interpretation of these data differs. Harmonisation will create a common understanding of the applicability of BCS-based biowaivers and the conditions of waiving, which in addition can be used also outside ICH countries developing and/or introducing BCS-based biowaivers.

Strategic Importance of the Topic

BCS-based biowaivers may prevent unnecessary exposure of mostly healthy volunteers to medicinal products. It will reduce the costs and time of developing, as *in vivo* studies to prove the biopharmaceutical quality of the medicinal product would not needed. Furthermore, it may be an effective way to facilitate introduction of medicinal products of good quality, especially in developing countries. Harmonisation would simplify the requirements by reducing *in vivo* studies, and therefore, facilitate the patient's access to medicines or post-approval changes.

Harmonisation would allow pharmaceutical companies to follow the same approach in all jurisdictions and help regulatory agencies in the timely authorization and availability of safe, effective and quality drugs based upon common and harmonised accepted criteria.

Type of Expert Working Group Recommended:

The EWG will require biopharmaceutic experts and clinical pharmacologists/pharmacokineticists to be nominated from the Members and Observers in line with the applicable Rules of Procedure.

Timing:

- Adoption of the topic by Approval of ICH Assembly — June 2016
- Agreement of Concept Paper and Business Plan by Informal WG — Aug. 2016
- Adoption of Concept Paper and Business Plan by MC — Sept. 2016
- First EWG meeting (Osaka, Japan) — Nov. 2016
- Adoption of *Step 2 a/b* Document — 1 - 2Q 2018
- Adoption of *Step 4* Document — 2Q 2019