M9: Biopharmaceutics Classification system-based Biowaivers

Step 4 document – to be implemented

Prepared by the ICH M9 Expert Working Group

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Legal Notice

Background

- This document has been signed off as *Step 4* document (20 November 2019) to be implemented by the ICH Regulatory Members
- This document was developed based on a Concept Paper (7 October 2016) and Business Plan (7 October 2016)

Key Principles

- This multidisciplinary Guideline addresses the Biopharmaceutics Classification System (BCS)-based waivers of bioequivalence studies (biowaivers).
- This Guideline provides recommendations on how to determine the biopharmaceutics classification of drug substances.
- In addition, the Guideline provides recommendations to support the waiver of bioequivalence studies for BCS Class I and III drugs.

Key Principles (continued)

- The BCS-based biowaiver is only applicable to immediate release, solid orally administered dosage forms or suspensions designed to deliver the 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.

Guideline Objectives

- The BCS-based biowaiver approach is intended to reduce *in vivo* bioequivalence studies.
- This Guideline
  - provides recommendations on the biopharmaceutics classification of drug substances, and to support BCS-based biowaivers for drug products.
  - aims to harmonise current regional guidance, reduces *in vivo* bioequivalence studies, and support streamlined global drug development.

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Outline

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  - criteria for drug product composition and *in vitro* dissolution performance
- **Annexes to the Guideline**
  - clarifications on Guideline recommendations

Scope

- BCS-based biowaivers are limited to immediate release, solid orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation.
- Fixed-dose combination products are considered eligible in cases where all drug substances fulfill the criteria.
- Prodrugs may be eligible when absorbed as the prodrug.
- Narrow therapeutic index drugs are excluded from consideration for a BCS-based biowaiver.

BCS: Classification criteria

- The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance, resulting in four 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

Criteria and support of solubility:

- A drug substance is considered highly soluble if the highest single therapeutic dose is completely soluble in 250 ml or less of aqueous media over the pH range of 1.2 – 6.8 at 37°C.
- If this criteria is not met, but the highest strength is soluble over the pH range, a biowaiver may be supported by dose-proportional PK (AUC and Cmax) over a range that includes the highest single therapeutic dose.
- The lowest measured solubility over this pH range (i.e. 1.2 – 6.8) is used to classify the drug substance solubility.

Criteria and support of solubility (cont.):

Experimental conditions to support solubility:

- shake-flask technique, or an alternate method, if justified;
- buffers at pH 1.2, 4.5, 6.8 and at the pH at which the lowest solubility of the drug is observed;
- test pH at beginning and at end of the experiment; pH should be adjusted, if necessary, to maintain the pH;
- at least 3 replicate determinations at each pH level should be applied, using a validated assay method;
- the drug substance should be stable in all media.

Criteria and support of permeability:

- A drug substance is considered highly permeable if ≥ 85% of the administered dose is absorbed.

- A conclusion of high permeability may be supported by:
  - an absolute bioavailability ≥ 85%;
  - ≥ 85% of the administered dose recovered in urine and/or feces as absorbed drug material;
  - results of validated *in vitro* Caco-2 permeability assays.

Criteria and support of permeability (cont.):

- To be noted:
  - Human *in vivo* data from published literature may be acceptable.
  - If mass balance or Caco-2 studies are used, data to support drug substance stability in the gastrointestinal tract should be provided.
  - Such stability data are not required in case of a mass balance study showing ≥ 85% of the administered dose recovered as unchanged drug in urine.

Eligibility of a drug product for a BCS-based biowaiver:

- **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 administered with water and designed to deliver the drug to the systemic circulation;**
  - **the drug product is the same dosage form and strength as the reference product;**
  - **criteria with respect to composition (excipients) and *in vitro* dissolution performance of the drug product are fulfilled.**

Drug product composition waiver criteria:

- **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 ± 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.**

See Table 1, section 3.1: excipient criteria expected to demonstrate similarity

In vitro dissolution waiver criteria:

- **Comparative *in vitro* dissolution experiments should use compendial apparatuses and validated analytical methods.**
- **Experimental conditions:**
  - **rotation speed: paddle (50 rpm) or basket (100 rpm);**
  - **pharmacopoeial buffers, at least pH 1.2, 4.5 and 6.8;**
  - **900 ml or less media (37°C);**
  - **at least 12 units of test and reference product for each dissolution profile;**
  - **organic solvents or surfactants are not allowed;**
  - **enzymes may be acceptable (gelatin cross-linking).**

In vitro dissolution waiver criteria (cont.):

- **For BCS Class I drugs:**
  both test and reference products should display either very rapid (≥ 85 % dissolved in ≤ 15 mins), or rapid and similar *in vitro* dissolution (≥ 85% dissolved in ≤ 30 mins, f2 ≥ 50) in all media.

- **BCS Class III:**
  both test and reference products should display very rapid (≥ 85% dissolved in ≤ 15 mins) *in vitro* dissolution in all media.

Annexes:

- **Annex I: Caco-2 cell permeability assay method considerations**
  - **Validation; should take into account:**
    - **suitability by proof of rank-order of probe compounds with proven correlation between *in vitro* permeability and extent of *in vivo* drug absorption in humans**
    - **confirmation of the monolayer integrity**
  - **Assay considerations, including confirmation of passive transport of test drug**
  - **Includes a listing of Examples of model drugs for permeability assay method validation (see table 2);**

Annexes (cont.):

- **Annex II: further information on the assessment of excipient differences**
  - **Includes flow charts to guide BCS-based biowaivers (see figure 1 and 2).**
  - **Includes examples of acceptable differences in amount of excipients**
- **Separate clarification annex in Question and Answer format**
  - **Addresses questions received during the public consultation**
  - **Includes exceptions to the Guideline and how they should be handled**

Conclusions

- **This harmonised guidance on the basic requirements for accepting and applying BCS-based biowaivers, avoid unnecessary exposure of healthy volunteers to drugs and the risk of blood sampling, accelerate drug development and approval and may lower costs significantly.**

Contact

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

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