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.
Table of Guideline Contents

- 1. Introduction
  - 1.1. Background and Objective
  - 1.2. Scope
- 2. Biopharmaceutics classification of the drug substance
  - 2.1. Solubility
  - 2.2. Permeability
- 3. Eligibility of a drug product for a BCS-based biowaiver
  - 3.1. Excipients
  - 3.2. In vitro dissolution
- 4. Documentation
- 5. Glossary
- Annexes

Outline

- Objectives and scope of the Guideline
- Biopharmaceutics classification of the drug substance
  - based on solubility and permeability
- Eligibility of a drug product for a BCS-based biowaiver
  - 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 $\geq 85\%$ of the administered dose is absorbed.

• A conclusion of high permeability may be supported by:
  • an absolute bioavailability $\geq 85\%$;
  • $\geq 85\%$ 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 $\geq 85\%$ 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:
    o 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
    o 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

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