BCS and Biowaivers Regulatory Update

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Biopharmaceutics Classification System

- **BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, BCS takes into account three major factors that govern the rate and extent of absorption from IR solid oral dosage forms: dissolution, solubility and intestinal permeability.**

BCS Guidance:

IR drug products

non-NTI drug products

Biowaiver

The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence of equivalence other than in vivo bioequivalence test.

For solid oral dosage forms, Biowaiver(s) is generally based on dissolution test(s).

Biopharmaceutics Classification System

- It is a framework for classifying drug substance based on its solubility and permeability
- Drug Substance (API) classified into 4 classes:
  - Class 1: Highly Soluble / Highly Permeable (HS/HP)
  - Class 2: Low Solubility / Highly Permeable (LS/HP)
  - Class 3: Highly Soluble / Low Permeability (HS/LP)
  - Class 4: Low Solubility / Low Permeability (LS/LP)
- It is a drug development tool to justify 'biowaiver' in conjunction with the dissolution of the drug product.

GL Amidon, H Lennernas, VP Shah, JR Crison. A theoretical basis for a biopharmaceutics classification system: The correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 12: 413-420, 1995

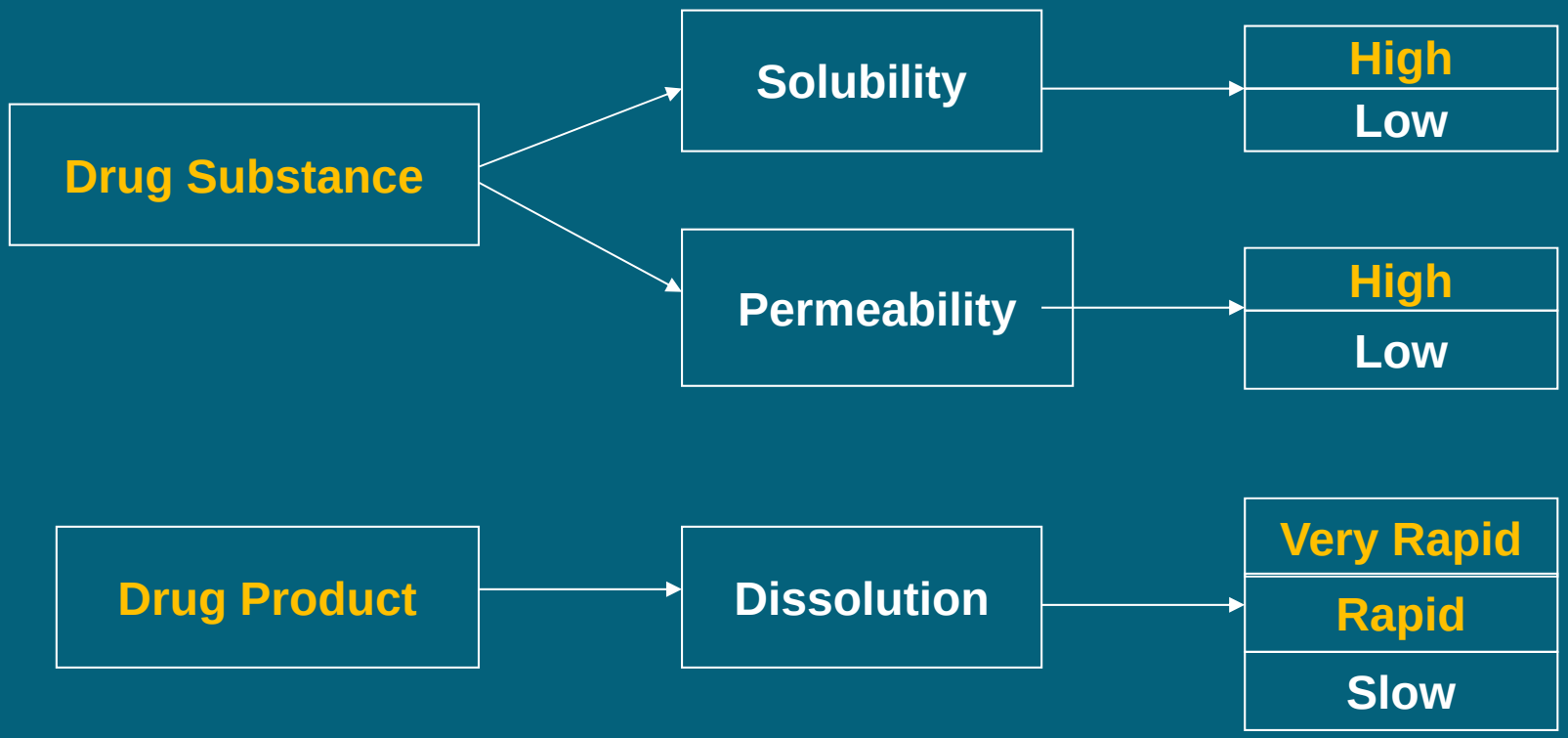
BCS - Solubility

- A drug substance should be classified as highly soluble when the highest strength is soluble in $\leq$ 250 mL of aqueous media over the pH range of 1.0 – 6.8
- pH conditions for solubility determinations can be based on the ionization characteristics of the test drug substance to include pH = pKa, pH = pKa+1, pH = pKa-1, pH = 1 & 6.8
- A minimum of three replicate determinations of solubility in each pH condition
- Solution pH should be verified after addition of drug substance to a buffer.
- Solution pH should be measured at the end of equilibrium solubility study.

BCS - Permeability

- Permeability is defined in terms of extent of absorption (fraction of the dose absorbed, not systemic BA) of a drug substance in humans, and directly on measurements of the rate of mass transfer across human intestinal membrane.
- A drug substance is considered to be highly permeable when the systemic BA or the extent of drug absorption in human is >85% of an administered dose based on mass balance determination or compared to intravenous dose.

Biopharmaceutics Classification System



Guidance for Industry

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

http://www.fda.gov/cder/guidance/index.htm

August 2000

Revised December 2017

FDA BCS Guidance August 2000 → BCS Guidance December 2017

Significant changes include:

- Addition of biowaiver for BCS Class 3 drugs (Biowaiver for BCS Class 1 and 3)
- Permeability boundary from 90% to 85%
- pH solubility range from 1 - 7.5 to 1 - 6.8
- Dissolution media volume from 900 mL to 500 mL
- Clarification of requirements for Fixed Dose Combinations and Orally Disintegrating Tablets
- Strengthen GI stability requirements

Biopharmaceutics Classification System (BCS)

Class 1 - HS/HP: Behaves like a solution, IVIVC Unlikely

Class 2 - LS/HP: Dissolution is rate limiting step; IVIVC may be possible

Class 3 - HS/LP: Permeability is rate controlling step; IVIVC Unlikely

Class 4 - LS/LP: Present significant problems for oral drug delivery; IVIVC ?

World Health Organization

Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability

WHO Technical Report Series, No. 937, 2006

Annex 7, p 347 – 390.

Revised: WHO Technical Report Series, No. 1003, 2017

Annex 6, p 181 – 236.

International Council for Harmonization (ICH) Biopharmaceutics Classification System-Based Biowaivers

M9 – draft June 2018.

BCS Based Biowaiver

- Well established excipients
- Excipients should NOT alter GI motility and drug absorption kinetics

  – Excipient is also present in comparator or

  – Excipient is present in a number of drug products having a registration in ICH-country

    - in amount usual for dosage form

    - FDA inactive ingredient database

Waiver of in vivo BA & BE for IR drug products based on BCS

Criteria for biowaiver for BCS Class 1 and 3 Drugs

- **Solubility:**
  - Highest strength soluble in 250 ml in pH 1.2 – 6.8
- **Permeability:**
  - For Class 1 extent of absorption greater than 85%
  - For class 3, permeability can be less than 85%.
- **Dissolution:**
  Basket method at 100 rpm or paddle method at 50 rpm (75 with justification) in 500 ml (900 with justification) in pH 1.2, 4.5 and 6.8.
  - Class 1: 85% or greater in 15 or 30 minutes
  - Class 3: 85% or greater in 15 minutes

  For biowaivers Test (multisource) and Reference (comparator) products must have similar dissolution profile (f_2) in all 3 media, pH 1.2, 4.5 and 6.8.

BCS Based Biowaivers
(Excipients)

- **BCS Class 1: HS/HP - VRD or RD**
  - Quantity of excipients should be consistent with intended function
  - When new excipient or atypically large amount of excipient is used, additional information documenting the absence of an impact on BA may be needed
- **BCS Class 3: HS/LP - VRD**
  - **c**ontains no inactive ingredients that are known to alter GI motility and/or absorption
  - **Inactive ingredients must be Q1 and Q2 (compared with RLD)**

Data to Support a Biowaiver Request

- **Data Supporting High Solubility**
  - Description of test method, analytical method and composition of buffer solutions
  - Test results – table and graphic presentation
- **Data Supporting High Permeability**
  - Human PK study design, method and data
  - Permeability method and criteria
- **Data Supporting Rapid, Very Rapid and Similar Dissolution.**
  - Description of the test method
  - Dissolution data with 12 units of T and R for each strength
  - Data supporting similarity profiles between T and R in all three media.

Dissolution Guidance
(IR, HS Drug Substance)

- **Dissolution Guidance:** Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances. August 2018

Dissolution Guidance
(IR HS Drug Substance)

- IR products with **highly soluble drug substance**
- Standard release test and criteria may be used in lieu of extensive method development and acceptance criteria-setting exercises.
- Establishes standard dissolution methodology and acceptance criteria for highly soluble drug substances
- No requirement to show discriminatory ability of the dissolution method for drug products with HS drug substance
- Follow BCS guidance to establish that the drug product contains highly soluble drug substance.
- Replaces draft dissolution guidance (for BCS 1,3) of Aug 2015.
- Drug substances that are not highly soluble, follow the recommendations in August 1997 dissolution guidance.

Dissolution Guidance – August 2018
(IR HS Drug Substance – BCS class 1 and 3)

Standard Dissolution Testing Conditions

- Basket Method (USP apparatus 1)
  - Stirring rate = 100 rpm
  - 500 ml. of 0.1N HCl in aqueous medium (900 ml with justification)
  - No surfactant in medium
  - 37 ± 0.5°C
- Paddle Method (USP apparatus 2)
  - Stirring rate = 50 rpm (75 rpm with justification)
  - 500 ml. of 0.1N HCl in aqueous medium (900 ml with justification)
  - No surfactant in medium
  - 37 ± 0.5°C
- **Dissolution Acceptance Criteria**
  - Q = 80% in 30 minutes

BCS-based Biowaiver Monographs Project - Overview

- **Genesis of biowaiver monographs**
- Project initiated by FIP/SIG Regulatory Science/FG - BCS and Biowaiver.
- No direct implication, no formal regulatory status, but represents best scientific judgment about eligibility for BCS based biowaiver. It provides a good starting point for the applicant. It is also used as a source of information by regulators.
- Drug substances selected based on WHO's List of Essential Medicines + other important drugs

Biowaiver Monographs

- Literature review - Solubility, permeability, dissolution, pharmacokinetic and bioequivalence data
  - Document summarizing all known relevant information
  - Review suggests feasibility of biowaiver for a generic
  - Indicates criteria for in vitro equivalence test.
  - Review can also indicate when biowaiver is not recommended, e.g., ciprofloxaxin, furosemide, mefloquin
- Published as a commentary in J Pharm Sci after peer review. Also on virtual special issue of J Pharm Sci.
- Available on FIP web page: www.fip.org
- More than 45 biowaiver monographs, ranging from BCS class 1- 4 have been prepared and published.

Impact of BCS-based S Biowaiver

- Lowers regulatory burden (IND/NDA/ANDA) without sacrificing the quality of the product
- Multisource drug products approved via BCS biowaiver procedure and manufactured under GMP can be assured to have same safety, efficacy and quality as the brand name product
- Reduces the cost of bringing generic product into the market
- Improves patient access to affordable medicines

Dissolution Based Biowaivers

- **Conventional Release Products**
  - Lower strengths, proportional formulations, f_2
  - BCS Class 1: HS/HP/RD
  - BCS Class 3: HS/LP/Very Rapidly dissolving
- **Extended Release Products**
  - Lower strengths, proportional formulations and same release mechanism
  - Beads in a capsule - Profile comparison in one medium
  - Tablets - Profile comparison in pH 1.2, 4.5, 6.8

Conclusions

- BCS principles provide a reasonable approach for drug product approval without sacrificing the drug product quality.
- BCS-based biowaiver (approved) generic products are considered TE and TI with brand name drugs.
- Biowaiver reduces regulatory burden without lowering drug product quality.

Thank You for Your Attention