Regulatory Updates: What is new in BCS and Biowaivers ?

Vinod P. Shah, Ph. D.
Pharmaceutical consultant
(Formerly with US FDA)
FIP/SIG Chair , Regulatory Sciences

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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 a dissolution test.

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

- Solubility is defined in terms of dose solubility, highest dose strength solubility in 250 ml of aqueous medium, pH 1.0-6.8.
- Classified as either high or low
  - High defined as dose/solubility volume less than or equal to 250 ml
  - Low defined as dose/solubility volume greater than 250 ml for any pH

BCS - Permeability

- Permeability is defined in terms of human permeability, absolute bioavailability (comparison with intravenous dose) or in terms of jejunum permeability.
- Highly permeable when the extent of drug absorption in human is >85% of an administered dose (compared to iv).

Biopharmaceutics Classification System (BCS)

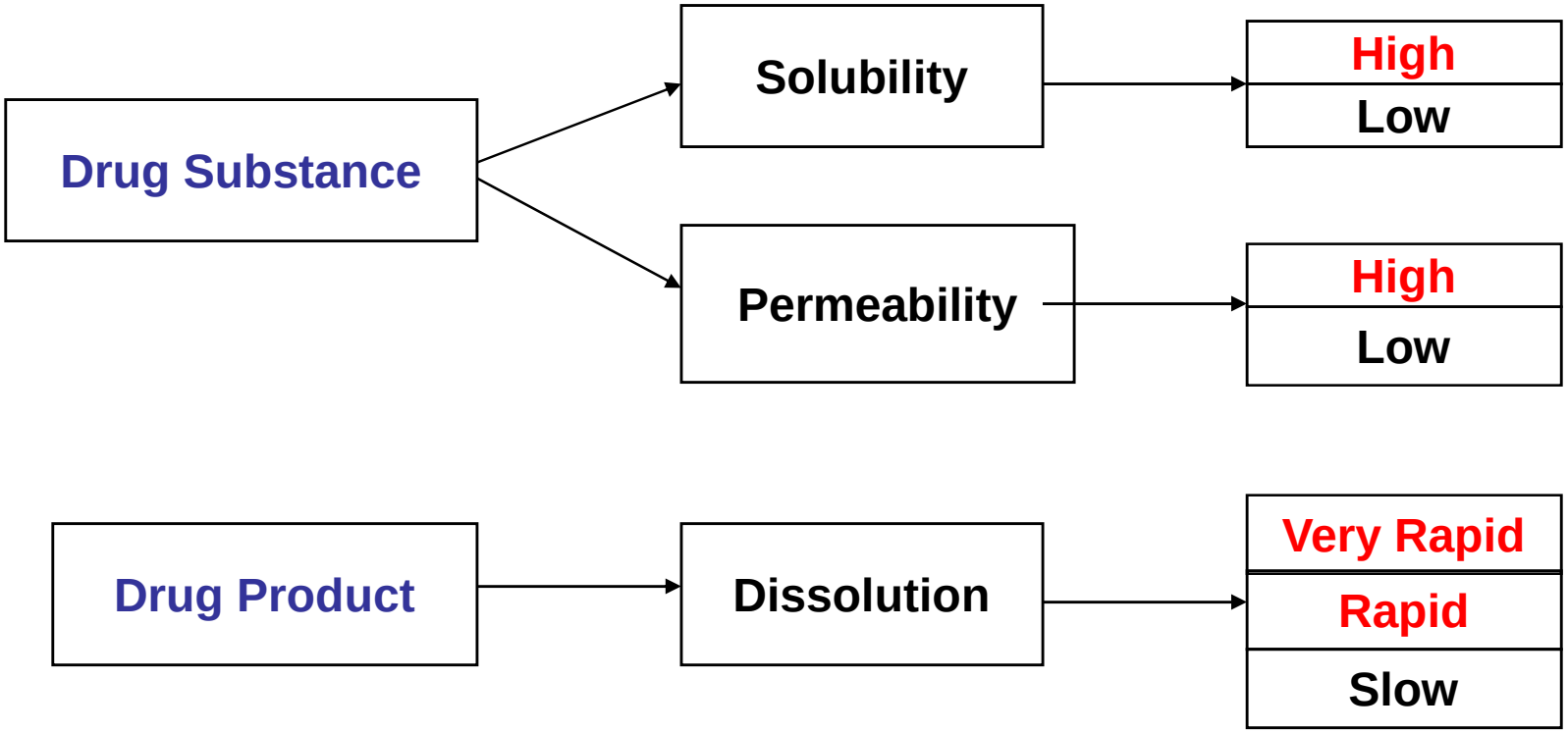
Class 1 - HS/HP: Behaves like a solution, IVIVC Unlikely

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 ?

Biopharmaceutics Classification System



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

- **Criteria for biowaiver**
  - Highly soluble: Highest dose soluble in 250 ml in pH 1.2 – 6.8
  - Highly permeable: extent of absorption greater than 85%
  - Rapidly dissolving: 85% or greater by basket method 100 rpm or paddle method 50 rpm in 900 ml in pH 1.2, 4.5 and 6.8
- **For a waiver of BE, T and R products should exhibit similar dissolution profile**

FDA Guidance - Waiver for Class 1 Drugs

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

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

Being Revised
Working Document – QAS/14.583 May 2014

Dissolution Test (BCS)

Multisource (test) and
Comparator (reference) product

•Paddle method at 75rpm (WHO) or 50rpm (FDA) or Basket method at 100 rpm in pH 1.2, 4.5, 6.8
•Dissolution profile similarity

Dissolution Characteristics:

•Very rapidly dissolving – 85% in 15 min
•Rapidly dissolving – 85% in 30 min
•Slowly dissolving – more than 30 min for 85% dissolution

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

BCS Related Guidance

- **BCS Guidance:** Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a biopharmaceutics classification system - **August 2000.**
- **Draft Guidance:** Update on the (above) BCS biowaiver guidance - **May 2015**
- **Draft Guidance:** Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and Class 3 Drugs - **August 2015.**

FDA BCS Guidance August 2000 → Draft BCS Guidance May 2015

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

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 (Highly soluble)
- **Permeability:**
  - For Class 1 extent of absorption greater than 85% (Highly permeable)
  - For class 3, permeability can be less than 85%.
- **Dissolution:**
  Basket method at 100 rpm or paddle method at 75 rpm in 500 ml of 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.

*** Based on Draft BCS Guidance, May 2015.**

BCS Based Biowaivers *

- **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)**

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.

*** Based on draft BCS Guidance, May 2015**

BCS Class 1 and 3 Dissolution Methodology & Specifications*

(After confirming BCS Class 1 or 3)

Dissolution Method

- Basket Method (USP apparatus 1)
  - 500 ml of 0.01M HCl aqueous media, 100 RPM, 37± 0.5 C
- Paddle Method (USP apparatus 2)
  - 500 ml of 0.01M HCl aqueous media, 75 RPM, 37± 0.5 C

Specification

- BCS Class 1: A single point dissolution specification of Q=80% in 30 minutes
- BCS Class 3: A single point dissolution specification of Q=80% in 15 minutes

*Based on Draft IR dissolution guidance for BCS class 1,3 drugs. Aug 2015

BCS-based Biowaiver Monographs Project - Overview

- **Genesis of biowaiver monographs**
- Project initiated by FIP/SIG - BCS;
  Now 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 can suggest feasibility of biowaiver for a generic formulation
  - 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 process. 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 Biowaiver Monographs

- Impact on approval of multisource (generic) drug products
- 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
- Lowers regulatory burden (IND/NDA/ANDA) without sacrificing the quality of the product
- Reduces the cost of bringing generic product into the market
- Improves patient access to affordable medicines

Biowaiver

Lower Strength(s)

- **Conventional Release Tablets/Capsules**
- **Extended Release Beaded Capsules**
- **Extended Release Tablets**

Biowaivers

Proportionally Similar

- All active and inactive ingredients are exactly in the same proportion
- Total weight remains nearly the same for all strengths (within ± 10% of total weight of the strength on which a biostudy was performed) and the change in strength is obtained by altering the amount of the active ingredient and one or more of the inactive ingredients.

Dissolution Based Biowaivers

- **Conventional Release Products**
  - Lower strengths, proportional formulations, f_2
  - BCS Class 1: HS/HP/RD
  - BCS Class 2: LS/HP, Weak acids, HS in pH 6.8
  - 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