BCS, Biowaivers and Dissolution Test Methodologies

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Outline

- BCS
  - Class 1 and 3
- Biowaivers
  - Conventional release - lower strengths
  - Modified Release - lower strengths
- Dissolution test methods
- Conclusions

BCS
Biopharmaceutics
Classification System

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

Biopharmaceutics Classification System

Solubility

- Solubility is defined in terms of dose solubility, highest dose strength solubility in 250 ml of aqueous medium, pH 1.0-6.8.
- Highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1.0-6.8.

Biopharmaceutics Classification System 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).

FDA 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- **Draft Guidance:** Update on the (above) BCS biowaiver guidance - **May 2015**
- **Draft Guidance:** Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and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

Global BCS Guidances

WHO

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

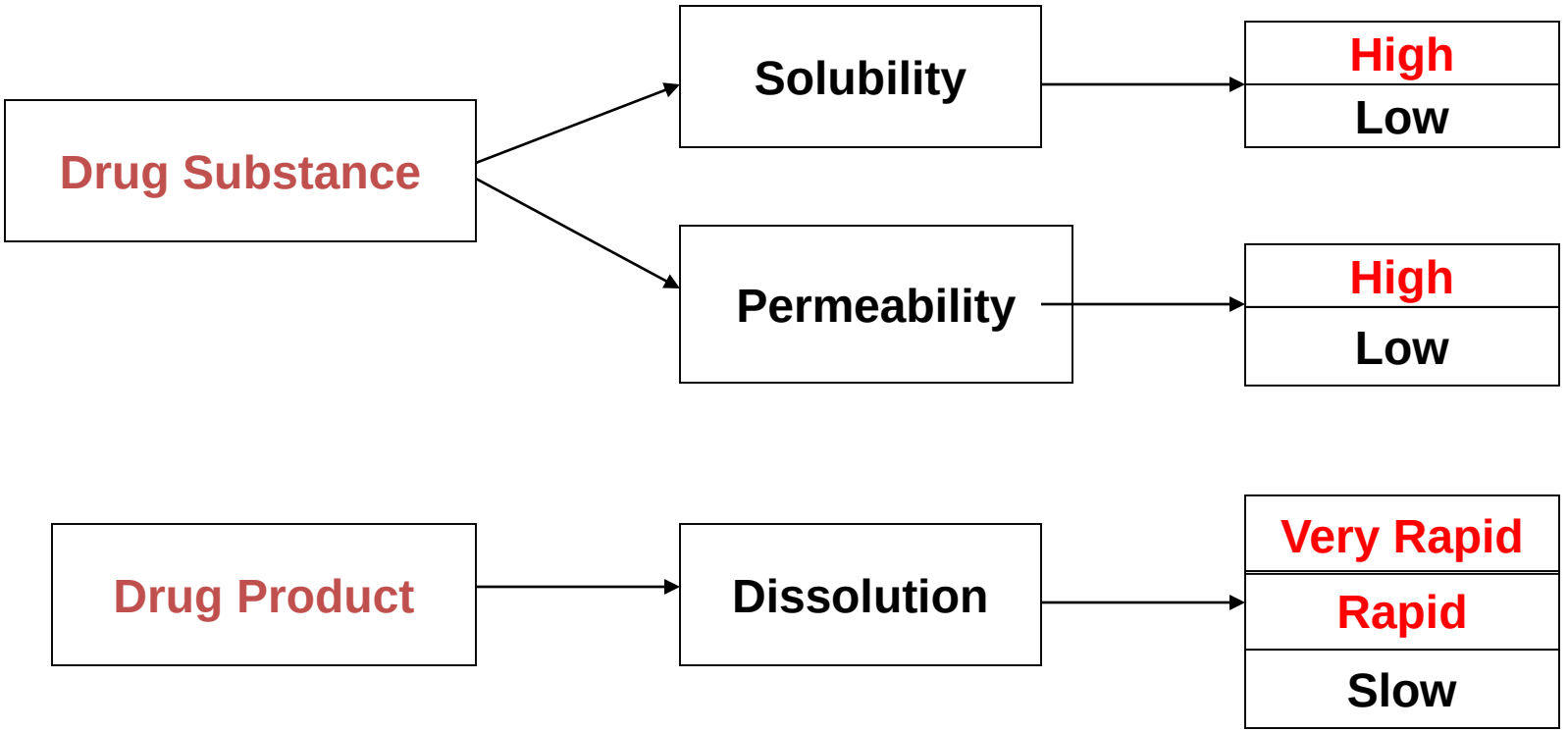
  WHO Technical Report Series, No. 937, 2006 : Annex 7, p 347-390.

  WHO Technical Report Series, No. 992, 2015: Annex 7, p 134-184.

EMEA

- European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP), guidance on the investigation of bioequivalence, 2010.

Biopharmaceutics Classification System



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

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 (HS)
- **Permeability:**
  - For Class 1 extent of absorption greater than 85% (HP)
  - For class 3, permeability can be less than 85%. (LP)
- **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

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.

Biowaivers

Principles employed for assessing biowaiver

- Biopharmaceutics Classification System
- In vitro in vivo correlation (Level A, B, C and D)
- Formulation proportionality and dissolution profile similarity (f_2)
- Quality by Design (QbD) Space
- In vitro release profile
- In vitro characterization

Biowaiver

Lower Strength(s)

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

Formulation Proportionality

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.

Immediate Release Drug Products

- Highest strength
  – approved based on BE study
- Lower strengths
  – dose proportional formulations
  biowaiver based on dissolution profile comparison.

Extended Release Drug Products

- Highest strength
  - approved based on BE study.
- Lower dose – Formulation proportional and same drug releasing mechanism
  – Beaded capsules: dissolution profile comparison with highest strength under one test condition
  – Tablets: dissolution profile comparison with highest strength in pH 1.2, 4.5 and 6.8

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

Biowaiver

- Lowering regulatory burden,
  provide regulatory relief without loss of drug product quality
- Product approved based on in vitro data

Conclusions

- BCS principles provide a reasonable approach for testing and approving drug products – BCS Class 1 and 3.
- Lowers regulatory burden, provides regulatory relief without loss of drug product quality.
- BCS also provides an avenue to predict drug disposition (BDDCS)
  - transport, absorption, elimination.
- Improves patient access to affordable medicines

Thank you for your Attention