School of Pharmacy

Faculty of Medicine

The Chinese University of Hong Kong

Workshop in Celebration of 25th Anniversary of the School of Pharmacy

Biopharmaceutics of Modified Release Products and Challenging Drug Molecules

Biowaivers: BCS and IVIVC

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Biowaivers

- What is a biowaiver?
- What are the various ways you can get biowaivers?
- BCS based biowaivers
- When is IVIVC useful as a biowaiver tool?

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

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

Dissolution

- In vitro characterization
- In vitro release profile

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.

Biopharmaceutics Classification System

BCS

Biopharmaceutics Classification System

- It is a framework for classifying drug substance based on its solubility and permeability
- It is a drug development tool to justify 'biowaiver' in conjunction with the dissolution of the drug product.
- It is a drug classification scheme that provides a basis for establishing IVIVC

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

• 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

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

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 ?

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

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

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 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.**

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**

In Vitro In Vivo Correlation

IVIVC

In Vitro - In Vivo Correlation

- **It is a functional or qualitative relationship between *in vitro* dissolution and *in vivo* bioavailability parameters.**
- **An optimum correlation is one in which *in vitro* dissolution is predictive of *in vivo* behavior of various lots of prodcuts in target population.**

In Vitro In Vivo Correlation

FDA Guidance for Industry

Extended Release Solid Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlations (September 1997)

FDA IVIVC Guidance

- FDA Guidance for Industry provides recommendations for properly establishing IVIVC of modified-release oral drug products
- IVIVC enhances drug product understanding during development.
- IVIVC defines the impact of each component and manufacturing step through *in vivo* studies
- IVIVC can be used to support post-approval changes, biowaivers and changes in dissolution method/specifications

In-Vitro - In-Vivo Correlation

- **Correlation:**
  - **One or more of *In-vivo* parameters are correlated with *In-vitro* release parameter of the product. This involves products which differ in *In-vivo* as well as *In-vitro* performance.**
  - **Differences in *In-vitro* release profile are reflected in differences in *In-vivo* performance of the product.**
  - **Minimum three products needed to see the correlation**
  - **With two products, it is rank order relationship.**
- **Association:**

  Acceptable *In-vivo* data are associated with acceptable *In-vitro* performance of the product.

In Vitro - In Vivo Correlation

Parameters

- ***In Vitro:*** **Dissolution profile, amount dissolved in specified time, dissolution rate.**
- ***In Vivo:*** **Cmax, tmax, AUC, Ae**
  % absorbed vs. time
- **Technique: Deconvolution, Moment Theory**

Knowledge of GI physiology, rate limiting step in absorption and site(s) of absorption may also help in *in vitro - in vivo* correlation determination.

Products differing in *in vivo* performance and in *in vitro* performance are essential to establish correlation.

In Vitro - In Vivo Correlation

Types of Correlation

Level A:
- **Point to point correlation**
- **Utilizing entire plasma level profile (deconvolution) and dissolution profile**
- ***In vitro* can be used as a surrogate for *in vivo***

Level B:
- **Utilizes all data, uses statistical moment theory. Do not cosider the shape of the curve.**

Level C:
- **Single parameter correlation.**

Mapping:
- **Response surface**

Level B, Level C and Mapping need at least three batches prepared by changes in critical manufacturing and formulation variables and studied *in vitro* and i*n vivo.*

In vitro - In Vivo Correlation

The most common process for developing IVIVC involves

- Developing at least three (3) formulations with different in vitro release rates,
- Determining their in vitro dissolution and in vivo plasma concentration profiles, and
- Establishing an in vivo time to allow correlation, based on deconvolution methods, between fraction dissolved vs. fraction absorbed.
- When a true dissolution condition independent formulation is involved, e.g., GIT whose dissolution is independent of pH and agitation, one formulation can be used to determine IVIVC.

Developing IVIVC

- **Objective**
  - Develop in vitro dissolution test that correlates with in vivo results
  - FDA level A correlation most desirable
- **Formulation**
  - Modified Release monophasic or multiphasic tablet
  - Products with three different release rates
    - **Fast**, **Intermediate** and **Slow**
- **Pharmacokinetics (PK)**
  - Single-dose cross-over study with all three formulations.
  - PK data deconvoluted with oral solution to provide in vivo absorption profile
- **IVIVC – Correlation?**

Developing IVIVC

- The method conditions can have a large impact on the "quality" of the IVIVC
  - Design of Experiments approach can efficiently optimize dissolution media selection and procedure
- Knowing the release mechanism
  - improves ability to select conditions that optimize correlation
  - enhances understanding of in vivo performance

In Vitro In Vivo Correlation

Formulation/Product Specific

- IVIVC developed for one product may not hold for another product
- Products differ in release mechanism
- Excipients and manufacturing process may be different
- Current approach is too simple: dissolution test conditions may not reflect GI physiology
  → Biorelevant dissolution test

Why do IVIVC ?

- Dissolution testing and plasma drug concentrations are identified as the most successful surrogate for safety and efficacy
- Reduction of regulatory burden: IVIVC in lieu of required *in vivo* studies, leading to:
  - Time/Cost savings during product development
    - Less testing in humans
- Permits setting wider than standard (±10%) *in vitro* release acceptance criteria

Applications of IVIVC

- Understanding key formulation variable(s)
- Biowaivers for changes in drug product
  - Lower strengths
  - New strengths
  - Changes in components and/or composition (within SUPAC guidelines)
    - Release rate controlling
    - Non-release rate controlling
  - Changes in manufacturing site, process and/or equipment (within SUPAC guidelines)
- Setting dissolution specifications
  - Justification of limits other than +/-10%

Benefits of IVIVC

- Provides framework for formulation development
- Promotes prioritization of formulation efforts toward compounds with bioavailability problems and improves communication across disciplines
- Places development of biorelevant dissolution method formally into development process
- Defines manufacturing parameters at an early stage in the development process and facilitates early transfer of formulation to manufacturing site
- Reduces the risk of requiring Phase III to market BE studies

Regulatory Application

- Biowaiver – preapproval manufacturing changes
- Post approval manufacturing changes
- Approval of lower strengths
- Wider in vitro specs

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

Biowaiver

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

Thank You for Your Attention