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?

Biowaivers: BCS and IVIVC

**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.

**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
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

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

World Health Organization

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

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 (f2) 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**
  - contains 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 (f2) in all 3 media, pH 1.2, 4.5 and 6.8.

* Based on draft BCS Guidance, May 2015
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 products in target population.

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**

**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 consider 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 *in vivo.*

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**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.

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**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?**

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
  \(\rightarrow\) 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