TO WAIVE OR NOT TO WAIVE

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BIOWAIVER

Waiver of *In Vivo* BE Studies... 
**Not** waiver of BE!
Regulatory Bioequivalence: 
An Overview

What do we mean with equivalence?
Pharmaceutical equivalence
Bioequivalence
Regulatory Bioequivalence: An Overview

Sometimes pharmaceutical equivalence is enough

- Aqueous solutions
  - Intravenous solutions
  - Intramuscular, subcutaneous
  - Oral solutions
  - Optic or ophthalmic solutions
  - Topical solutions
  - Solutions for nasal administration

- Powders for reconstitution as solution

- Gases for inhalation

“Self-evident” - Biowaivers granted
Condition: excipients do not alter absorption / disposition / viscosity
Regulatory Bioequivalence: An Overview

Sometimes it is not enough

Pharmaceutical equivalence by itself does not necessarily imply therapeutic equivalence
Regulatory Bioequivalence: An Overview

METHODS FOR DEMONSTRATING BE

- In vivo testing in humans, using a pharmacological response (pharmacodynamic endpoint)
- Well controlled clinical trials in humans that establish the safety and effectiveness of the drug product.
- An in vivo test in humans in which the concentration of the active ingredient or metabolite in an accessible biological fluid is measured as a function of time
- In vitro methods (e.g., dissolution)
  - BIOWAIVERS
Biowaivers

Biowaivers are granted on the basis of:

- Composition Proportionality– based on:
  - acceptable BE studies on the highest strength
  - Proportional similarity of the formulations across all strengths
    (Qualitatively same, Quantitatively proportional)
  - Manufactured by same manufacturing process
  - Acceptable in vitro dissolution testing of all strengths
  - Linear pharmacokinetics

- In Vivo In Vitro Correlation
  - Based on correlation between in vitro data and in vivo profile

- Biopharmaceutics Classification System
  - Considers the solubility, permeability and dissolution behaviour
Biowaivers and the Biopharmaceutics Classification System

BCS was introduced in 1995 by the US FDA

• First aim: granting biowaivers for Scale-Up and Post-Approval Changes (SUPAC).
  e.g. Changes in excipients, manufacturing site…
  ⇒ A simple dissolution test (comparison) could be accepted as surrogate

• Second aim: more recently, extension of the BCS concept for approval of oral generic products.
Biowaivers and the Biopharmaceutics Classification System

BCS as a Prognostic tool in oral drug product development


BCS as Precursor classification tool for the BDDCS

- Wu CY, Benet LZ. *Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a Biopharmaceutical Drug Disposition Classification System.* Pharm Res. 2005: 22(1)
Biowaivers and the Biopharmaceutics Classification System

BCS - Prognostic tool in Oral drug product development:

• Identify the RLS in the intestinal absorption process

• Discovery and early development of NME

• BA/BE standards for IR oral drug product approval (FDA, EMA, WHO)
  – Waiver of *In Vivo* BE Studies
  – Objective of biowaivers: lower the regulatory burden without loss of drug product quality
Biowaivers and the Biopharmaceutics Classification System

BCS as a precursor classification tool for BDDCS

- Drug disposition of NME
- Effects of efflux and absorptive transporters on oral absorption
- Food-drug effects
- Potential drug-drug interactions in the intestine and/or liver
Biopharmaceutics classification system – Scientific Rationale

Permeability of the drug through GI membrane
Solubility/dissolution of the drug dose in the GI milieu

- **Rapid dissolution** - ensure that in vivo dissolution is not likely to be the “rate determining” step
- **High solubility** - ensure that solubility is not likely to limit dissolution and, therefore, absorption
- **High permeability** - ensure that drug is completely absorbed during the limited transit time through the small intestine
Biopharmaceutics classification system – Scientific Rationale

Objective: Predict in vivo pharmacokinetic performance of drug products

Biopharmaceutics classification system – Scientific Rationale

BCS takes a mechanistic approach to setting BE standards: mass transport in the GI tract

Absorption Rate = \( \frac{dm}{dt} = \int \int_A P_w C_w dA \)

\[ M(t) = \int_0^t \int_A P_w C_w dAdt \]

Amidon, 1995
Biopharmaceutics classification system – Scientific Rationale

- If two drug products containing the same drug, have the **same concentration time profile** at the intestinal membrane surface, then they will have the same rate and extent of absorption.

⇒ if two drug products have the same **in vivo dissolution profile under all luminal conditions**, they will have the same rate and extent of drug absorption.
Biopharmaceutics classification system – Scientific Rationale

The science of BE is at the absorption site

Similar in vivo dissolution $\rightarrow$ similar plasma levels

*In vitro dissolution* $\rightarrow$ *in vivo dissolution*

Note:
- In Vitro dissolution methodology must capture the most important rate controlling in vivo dissolution process
- Post-absorption events (MTB, enterohepatic recycling) can result in complex and variable pharmacokinetic profiles – with little relevance to drug product quality /BE.
- 60% of HVDs – highly variable due to drug substance PK characteristics rather than drug product characteristics (AAPS J, 2008)
Biopharmaceutics classification system

- Scientific framework which divides APIs into four groups, according to their solubility and their permeability properties. (Amidon et al., 1995)

<table>
<thead>
<tr>
<th>High Solubility</th>
<th>Low Solubility</th>
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</thead>
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<tr>
<td>High solubility</td>
<td>Low solubility</td>
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<tr>
<td>High permeability</td>
<td>High permeability</td>
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<td>IVIVC if dissolution rate &lt; GE rate</td>
<td>IVIVC if in vitro dissolution rate ~ in vivo dissolution rate</td>
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<tr>
<td><strong>Class 3</strong></td>
<td><strong>Class 4</strong></td>
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<tr>
<td>High solubility</td>
<td>Low solubility</td>
</tr>
<tr>
<td>Low permeability</td>
<td>Low permeability</td>
</tr>
<tr>
<td>Limited or no IVIVC</td>
<td>Limited or no IVIVC</td>
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</tbody>
</table>
Biopharmaceutics classification system
Eligibility criteria for biowaiver - Oral generic drugs

✓ BCS classification of the API: solubility and permeability
✓ Dissolution characteristics
✓ Nature of the excipients - may influence motility and/or permeability in the gastrointestinal tract.
✓ Therapeutic Index
✓ Formulation: product not designed to be absorbed from the oral cavity and not MR
✓ Risk assessment: To be performed only if an incorrect biowaiver decision is likely to create a risk for the patient
Biopharmaceutics classification system

☑ BCS classification of the API: solubility and permeability

- **Class 1**
  - Highly permeable
  - Highly soluble

- **Class 2**
  - Highly permeable
  - Poorly soluble

- **Class 3**
  - Poorly permeable
  - Highly soluble

- **Class 4**
  - Poorly permeable
  - Poorly soluble
Biopharmaceutics classification system

✓ BCS classification of the API: solubility and permeability

• High Solubility
  – the highest dose strength is soluble in <250 mL aqueous buffers over pH range of at 37°C.
    pH range of 1-7.5 at 37 ± 1 °C (FDA)
    pH range of 1-6.8 at 37 ± 1 °C (EMA)
    pH range of 1.2-6.8 at 37 ± 1 °C (WHO)

• High Permeability
  – Pharmacokinetic Studies in Human:
    • Mass Balance Studies
    • Absolute BA Studies - extent of absorption in humans is determined to be ≥ 90% (FDA), ≥ 85% (EMA, WHO)
  – Intestinal Permeability Methods
    • monolayers of suitable epithelial cells, e.g. Caco-2 cell line
Biopharmaceutics classification system

Class 1
Highly permeable
Highly soluble

Transporter effects minimal

- Eligible for biowaivers, FDA, EMA, WHO

Excipient / extent of BA
- FDA: qty consistent with intended function
- EMA: Excipients that might affect BA are qualitatively and quantitatively the same.
Class 2
Highly permeable
Poorly soluble

Eligible for Biowaivers (WHO):
- dose: solubility ratio ≤ 250 ml at pH 6.8
- Rapidly dissolving ≥ 85% in 30 min (pH 6.8)
- Similar dissolution profile vs comparator (pH 1.2, 4.5, 6.8)

Oral availability of the API depends on the formulation and manufacturing method.
Class 3
Poorly permeable
Highly soluble

Absorptive transporter effects predominate

Eligible for biowaivers (EMA, WHO)

- Product is very rapidly dissolving
- Excipient effects on uptake transporters
  Excipients that might affect BA are qualitatively and quantitatively the same
  AND other excipients are qualitatively the same and quantitatively very similar.

Biopharmaceutics classification system

<table>
<thead>
<tr>
<th>Class 3</th>
<th>Absorptive transporter effects predominate</th>
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<td>Atenolol</td>
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<td>Atropine</td>
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<td>Bisphosphonates</td>
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<td>Zalcitabine&lt;sup&gt;U&lt;/sup&gt;</td>
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</tbody>
</table>
Biopharmaceutics classification system

Class 4
- Poorly permeable
- Poorly soluble

Absorptive and Efflux transporter
- Effects could be important

- Not eligible for biowaivers
- BA is minimal

Class 4
- Acetazolamide
- Aluminum hydroxide
- Amphotericin
- Chlorthalidone
- Chlorothiazide
- Ciprofloxacin
- Colistin
- Digoxin
- Furosemide
- Neomycin
- Nystatin
- Ofloxacin
- Phenazopyridine
- Talinolol
DISSOLUTION TESTING:
SOUL OF BIOWAIVERS

• Different from compendial testing
  – Media: 900mL: pH 1-1.2, 4.5, 6.8
  – Number of units tested: 12
• Minimum 3 time-points for both profiles
• Sampling schedule: 10, 15, 20, 30 and 45 min
• Apparatus: Rotating basket (100 rpm), rotating paddle (50 rpm)
• Comparative dissolution profile
• Acceptance criteria:
  Class 1: very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min)
  Class 3: very rapid (> 85 % within 15 min)
The Biowaiver Monographs

- An initiative of the Federation Internationale Pharmaceutique (FIP).

- The aim is to evaluate all relevant data from the literature, for a given API, to assess the risk associated with a biowaiver
  - RISK = probability of an incorrect biowaiver decision
  - RISK = consequences of an incorrect biowaiver decision in terms of public health and individual patient risks.
  - RECOMMENDATION = Biowaiver

- No formal regulatory status but represents the best current scientific opinions

- The approach includes all factors considered in the WHO Document:
  "Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms."
The Biowaiver Monograph

What is taken into consideration?

- Physicochemical properties, especially solubility at 37°C between pH 1.2 and 6.8, but also pKa, logP, polymorphism, solvates and salts. If necessary, additional solubility and dissolution studies are run with the pure API.

- Determinations of Permeability e.g. \( B_{\text{abs}} \), urinary excretion, Caco-2 studies.

- Literature studies on bioequivalence of existing products.

- Interactions with food and excipients.

- Literature and laboratory data comparing dissolution of existing products.
The Biowaiver Monograph
Evaluation of the collected information

- BCS Class (II, III, IV)
- narrow therapeutic index
- „critical“ indication
- Risk of abuse
- slow and incomplete dissolution
- „Food effects“ or interaction with excipients
- published bioequivalence

- BCS Class I (II, III)
- wide therapeutic index
- „uncritical“ indication
- no risk of abuse
- „rapid“ or „very rapid“ dissolution
- no reported interaction with food or excipients
- BE-Studies

Prof. Dr. Jennifer Dressman & Corina Becker, 2007
# Biowaiver Monographs already available

- Acetaminophen = Paracetamol
- Acetylsalicylic acid
- Amitriptyline Hydrochloride
- Atenolol
- Acetzolamide
- Aciclovir
- Amodiaquine Hydrochloride
- Bisoprolol fumarate
- Chloroquine Phosphate
- Chloroquine Hydrochloride
- Chloroquine Sulfate
- Cimetidine
- Codeine phosphate
- Diclofenac Sodium
- Efavirenz
- Fluconazole
- Ibuprofen
- Ketoprofen
- Levetiracetam
- Mefloquine Hydrochloride
- Metronidazole
- Prednisolone
- Primaquine Diphosphate
- Pyrazinamide
- Quinine Sulfate
- Rifampicin
- Verapamil Hydrochloride
- Zidovudine (Azidothymidine)

[www.fip.org/bc](http://www.fip.org/bc)
COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Ciprofloxacin Hydrochloride

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Published online 2 July 2010 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.22258

ABSTRACT: Literature data relevant to the decision to allow a waiver of in vivo bioequivalence
**Additional source for BCS classification**

- Therapeutic Systems research Laboratory (TSRL Inc., Ann Arbor, MI) [http://www.tsrlinc.com/services/bcs/search.cfm](http://www.tsrlinc.com/services/bcs/search.cfm)

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<td><img src="image" alt="Ibuprofen structure" /></td>
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<tr>
<td>WHO</td>
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</table>
A decade of biowaivers - FACTS

- No incidents of Type I errors in the use of in vitro testing to assess BE of Class 1 drugs in the USA and EU. (Mehta 2002, 2007)

- Clinical performance of the majority of approved IR oral drug products essential for human health can be assured with an in vitro dissolution test (Dahan et al, AAPS J. 2009)
Conclusion

Biowaivers

- Based on scientific principles
- Avoid unnecessary human experiments
- Reduce cost and time of developing generic IR oral drug products
- Enhance the efficiency in drug development and regulatory approval processes
- BCS provides an invaluable tool in drug discovery, development, and regulation.
Challenges

• Barriers that limit biowaiver application
  – Lack of international regulatory harmonization
  – Uncertainty in regulatory approval
  – Organizational barriers

• New regulatory policies, with criteria and class boundaries that will allow granting an in vivo biowaiver to larger number of drugs.
THANK YOU