BCS-based biowaivers
Industry perspective
User View

Martina Nora Odlozilikova
The Biopharmaceutics Classification System (BCS) is a theoretical framework for classifying drugs based on their solubility and permeability.

**CLASS I**
- High solubility
- High permeability

**CLASS II**
- Low solubility
- High permeability

**CLASS III**
- High solubility
- Low permeability

**CLASS IV**
- Low solubility
- Low permeability

Drugs like Pregabalin, Metformin, Atorvastatin, and Aprepitant are classified according to their solubility and permeability properties.

---


Sept 26-27th 2019, BioBridges, Prague
ICH M 9 draft: Comments

General comment:
“...approach not fully in line with the guideline should be supported when convincing justification provided.”

Specific comments [lines]:
• Different salts not possible [67-68]
• Moderate permeable compounds (50–84%) regarded as poorly permeable [176-178]
• Strictly set dissolution conditions [197-203]
• BCS-based strength biowaiver [250-251]
FINAL ENDORSED CONCEPT PAPER: Where the targets met?

**Issues to be resolved**
- Supportive data for classification
  a) solubility
  b) permeability
- Supportive data for a waiver
  a) dissolution
  b) excipients

**Additional issues**
- Different criteria for dissolution
- BCS-based strength biowaver
Points For Consideration

- Dose vs Strength
- Solubility methodology
- Degradation of API
- Comparator suitability
- BCS-based biowaivers in drug approvals
- Case studies
Solubility: Highest Single Dose versus Highest Strength

(Reality versus Theory or vice versa?)

**BCS shift from I/III into II/IV**
- verapamil, metoclopramide, ...

**Additional data**
- dose proportional pharmacokinetics
  (i.e. AUC and $C_{\text{max}}$) over a dose range that includes the highest therapeutic dose

**Critical dose evaluation?**

## Solubility: Experimental conditions

- **Equilibrium saturated solubility**
- **the check of pH and adjustment if necessary to ensure the specified pH**
- **Validated stability indicating method**
- **Degradation less than 10%**

### Degradation less than 10%: What is the relevant time frame?
- Over the extent of the solubility assessment – i.e. 24 hours?
- or
- Alignment with permeability specification? (i.e. 1 hour in gastric fluid + 3 hours in intestinal fluid)

### Praxis:
- volume 250 mL...uneconomical for highly soluble APIs
- pH change reported but not adjusted consequently
- employment of UV spectral method with no capability of degradation observation

**Dexamethasone:** neutral molecule, highly soluble, no pH-dependency expected, however at pH 4.5, 2- and 3-folded higher solubility than at pH 1.2 and 6.8 observed
Perform 24 h solubility determination at all pH values recommended in the regulatory guidance document.

Does the API show degradation at any pH value considered?

Yes:
- Perform degradation study (e.g. stability-indicating solubility determination) at this pH.

No:
- Solubility classification of the API according to the BCS criteria using 24 h solubility values.

Is it necessary to know the solubility value of the API in the media showing degradation to assign a BCS classification?

Yes:
- Perform additional solubility experiments using a shorter time period (e.g. 1 h at pH 1.2; 3 h at pH 6.8).

No:
- Solubility classification of the API according to the BCS criteria using 24 h solubility values. Report and discuss extent of observed degradation.

Solubility classification of the API according to the BCS criteria using 24 h solubility values. Report and discuss extent of observed degradation.
Solubility: WHO Draft Protocol

Experimental design

• shake flask method, 24 hours temperature, composition of buffers, three fixed pH
• Preliminary assessment (equilibrium & stability)
• Pivotal experiment
• Validated method to observe degradation
• Recommendation for the analytical method
### WHO: General Notes on Biopharmaceutics Classification System (BCS)-based Biowaiver Applications (2019)

....for products containing APIs for which PQTm has assigned a BCS classification..., a BCS-based biowaiver application can be made without providing data for classification of the API.

<table>
<thead>
<tr>
<th>Active pharmaceutical ingredient (API)</th>
<th>Therapeutic group</th>
<th>Highest single dose [mg]</th>
<th>BCS Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (as sulfate)</td>
<td>Antiretroviral</td>
<td>600</td>
<td>III</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Antiretroviral</td>
<td>200</td>
<td>I</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Antiretroviral</td>
<td>300</td>
<td>III</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Antiretroviral</td>
<td>40</td>
<td>I</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Antiretroviral</td>
<td>300</td>
<td>I</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Antibacterial</td>
<td>600</td>
<td>I</td>
</tr>
<tr>
<td>Fluconazole* (Polymorphs II &amp; III)</td>
<td>Antifungal</td>
<td>800</td>
<td>I</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Anti-tuberculosis</td>
<td>400</td>
<td>III</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Anti-tuberculosis</td>
<td>300</td>
<td>III</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Anti-tuberculosis</td>
<td>750</td>
<td>I</td>
</tr>
<tr>
<td>Moxifloxacin (as hydrochloride)</td>
<td>Anti-tuberculosis</td>
<td>400</td>
<td>I</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Anti-tuberculosis</td>
<td>400</td>
<td>I</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Anti-tuberculosis</td>
<td>500</td>
<td>III</td>
</tr>
<tr>
<td>Diethylcarbamazine</td>
<td>Anti-parasitic</td>
<td>500</td>
<td>III**</td>
</tr>
<tr>
<td>Misoprostol (as 1% dispersion in HPMC)</td>
<td>Prostaglandin analogue</td>
<td>0.8</td>
<td>III**</td>
</tr>
</tbody>
</table>
WHO vs FDA vs EMA: Is there a space for harmonized approach?

<table>
<thead>
<tr>
<th>API</th>
<th>BCS class</th>
<th>FIP monograph (year)</th>
<th>Product specific guidance (BCS-based biowaiver option)</th>
<th>Alignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir sulfate</td>
<td>III</td>
<td>Under preparation</td>
<td>FDA 2008 / not mentioned</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>I</td>
<td>Under preparation</td>
<td><strong>FDA 2010 / eligible</strong> EMA / as FDC eligible</td>
<td>✓</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>III</td>
<td>2011</td>
<td>FDA 2008 / not mentioned</td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>I</td>
<td>2011</td>
<td>FDA 2008 / not mentioned</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>I</td>
<td>2013</td>
<td>FDA 2008 / not mentioned</td>
<td></td>
</tr>
<tr>
<td>Fluconazol</td>
<td>I</td>
<td>2014</td>
<td>FDA 2018 / not mentioned</td>
<td>❗️</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>III</td>
<td>2008</td>
<td>FDA 2017 / not mentioned</td>
<td>❗️</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>III</td>
<td>2007</td>
<td>FDA 2008 / not mentioned</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>I</td>
<td>2011</td>
<td><strong>FDA 2010 eligible</strong></td>
<td>✓</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>I</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>I</td>
<td>Under preparation</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>III</td>
<td>---</td>
<td>FDA draft 2016 / not mentioned</td>
<td></td>
</tr>
<tr>
<td>Diethylcarbamazine</td>
<td>III</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Misoprostol</td>
<td>III</td>
<td>---</td>
<td>FDA 2010 / not mentioned</td>
<td></td>
</tr>
</tbody>
</table>
3. COMPARATOR PRODUCT SUITABILITY

Identification by PQTm of an API to be eligible for a BCS-based biowaiver application is made purely on the solubility, absorption, safety and related properties of the API (Class I or Class III). It does not imply that the recommended comparator product(s) will be rapidly dissolving in the case of Class I APIs or very rapidly dissolving in the case of Class III APIs, which is a requirement for BCS-based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the PQTm website is indeed suitable for a BCS based biowaiver application before product development.

Note that rapidly dissolving, or very rapidly dissolving, properties of a product are not required for in vivo bioequivalence studies. Thus, though a listed comparator product may not be suitable for BCS-based biowaiver purposes, it is still suitable for in vivo bioequivalence studies.

• The need for internationally acknowledged comparator list: smiley similar performance of generic medicines around the globe could be ensured

• ICH harmonized approach of BCS-based biowaivers?

BCS-based Biowaiver Role in Drug Approvals

EMA Product specific guidance permitting BCS-based biowaiver

<table>
<thead>
<tr>
<th>BCS 1</th>
<th>BCS 3</th>
<th>Data to be generated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agomelatine</td>
<td>Aliskiren</td>
<td>Entecavir</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Tenofovir disoproxil</td>
<td>Imatinib (possible BCS 1)</td>
</tr>
<tr>
<td>Memantine</td>
<td>Sunitinib</td>
<td>Lenalidomide (possible BCS 1)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td></td>
<td>Miglustat</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td></td>
<td>Oseltamivir (possible BCS 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Telithromycin</td>
</tr>
</tbody>
</table>
CASE STUDY: LENALIDOMIDE CAPSULES 25 MG

Lenalidomide hard gelatine capsules 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg product-specific bioequivalence guidance

Disclaimer:
This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)*

<table>
<thead>
<tr>
<th>BCS Classification**</th>
<th>BCS Class: □ I □ II □ Neither of the two</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background: Lenalidomide is a compound with complete absorption but the available data on solubility does not allow an BCS classification. If the applicant generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, lenalidomide could be classified as BCS class I drug and a BCS biowaiver could be applicable.</td>
<td></td>
</tr>
</tbody>
</table>

Bioequivalence study design
in case a BCS biowaiver is not feasible or applied

- single dose
- cross-over
- healthy volunteers
- □ fasting □ fed □ both □ either fasting or fed
- Strength: 25 mg
- Background: Highest strength to be used for a drug with linear pharmacokinetics with limited information

+ FDA product specific guidance from 2013 does not mention the BCS-based biowaiver possibility

BCS class 1 demonstrated
D/S ratio 73.5 for pH 6.8
Absorption complete (<90% recovered unchanged in urine)
<85% dissolved in 15 min in all media
Excipients: qualitatively the same

Alswisi, M. et al., Biopharmaceutics Classification System Based Biowaiver Studies of Lenalidomide Capsules (25 mg) – An Alternative to In vivo Bioequivalence Studies for Generic Oncology Drug Products. Journal of Bioequivalence & Bioavailability, 2019

Sept 26-27th 2019, BioBridges, Prague
BCS-based Biowaiver Role in Drug Approvals – cont.

CASE STUDY: PEDIATRIC ORAL SUSPENSION CONTAINING BCS CLASS 1 ANTIPYRETICS

ICH M9 draft guideline:
• BCS-based biowaiver applicable to immediate release, solid orally administered dosage forms or suspensions designed to deliver drug to the systemic circulation

• Lacking
  - Necessary adjustments to dissolution methods
  - Excipients variation

SmPC of the marketed “reference” products
• Posology 2.5–10 mL every 4 hours or
• 10–20 mg/kg body weight

Reasonable sample size for comparative dissolution testing?

x FDA dissolution database
x USP monograph

Sept 26-27th 2019, BioBridges, Prague
CASE STUDY 1: cont.

EMA Product specific BE guidances general note to BCS-based biowaivers:

However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III...either for test or reference, or unacceptable differences in the excipient composition.
CASE STUDY 1: cont.

### Composition of the reference products
(Different market and MAH)

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Qualitative Composition</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference 1</td>
<td>Reference 2</td>
</tr>
<tr>
<td>API</td>
<td>2.4 mg</td>
<td>2.4 mg</td>
</tr>
<tr>
<td>Excipients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorbitol</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Sorbitol liquid</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Maltitol liquid</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Citric acid</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Malic acid</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Flavour</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Colorant</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>NIPASEPT</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Water qs to</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

### Physicochemical properties of TEST
- pH comparable
- density comparable
- viscosity comparable

### Design of dissolution comparability testing
- 3 pH, paddle, 50 rpm
- criteria > 85% in 30 min
CASE STUDY 1: cont.

Results of dissolution testing at 50 rpm with the reference product

1. Great batch to batch variability
2. Sample not dispersed in the medium
3. Less than 85% in 30 min
4. Sample volume dependent rate of dissolution

So is there a space for dissolution method development with appropriate justification?

1. Higher rotation speed
2. Sample introduction to ensure dispersion of the product
3. Sample volume determination (considering that the highest single dose is 12.5 mL)
Comment:

In the draft ICH guideline, the conditions for dissolution testing particularly the rotation speed (i.e. paddles 50 rpm, basket 100 rpm), are strictly set. In the current EMA bioequivalence guideline where only “usual” experimental conditions are defined there is a possibility for justification when the conditions used are different. For example, in some cases of oral suspensions containing BCS class I substances, rapid dissolution cannot be obtained under conditions prescribed by the draft (i.e. paddles 50 rpm) for the test as well as for the reference due to the high viscosity of the formulation. The case-by-case approach should be justifiable when assessing the suitability of dissolution conditions for BCS-based biowaiver.

Proposed change:

The following conditions should be employed (unless otherwise justified) in the comparative dissolution studies to characterize the...
CASE STUDY 2: BCS 1 Cardioselective Beta-Blocker

Indications as per SmPC (reference product)

- Hypertension
- Ischemic heart disease (angina pectoris)
- Stable chronic heart failure with decreased systolic function of left ventricle; concomitant therapy with ACE inhibitors, diuretics and eventually with heart glycosides.

- Strengths: 10/5/2.5 mg

- Composition: not dose-proportional (amount of filler changed in account for the active substance) = mass equivalent
- film-coated tbl versus conventional

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose microcrystalline</td>
<td>+</td>
</tr>
<tr>
<td>Silica, colloidal anhydrous</td>
<td>+</td>
</tr>
<tr>
<td>Maize starch</td>
<td>+</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>+</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>+</td>
</tr>
<tr>
<td>Calcium hydrogen phosphate, anhydrous</td>
<td>+</td>
</tr>
</tbody>
</table>

Similar qualitative composition

Sept 26-27th 2019, BioBridges, Prague
CASE STUDY 2: cont.

<table>
<thead>
<tr>
<th>Strength</th>
<th>Dissolution results (pH 1.2, 4.5, 6.8)</th>
<th>Conclusion on similarity (T x R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>&gt; 85% in 15 min</td>
<td>similar</td>
</tr>
<tr>
<td>5 mg</td>
<td>&gt; 85% in 15 min</td>
<td>similar</td>
</tr>
<tr>
<td>2.5 mg</td>
<td>&gt; 85% in 30 min</td>
<td>F2 = 31</td>
</tr>
</tbody>
</table>

REFERENCE

<table>
<thead>
<tr>
<th>test medium</th>
<th>comparator</th>
<th>f2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 M HCl</td>
<td>R 5 mg</td>
<td>47.5</td>
</tr>
<tr>
<td></td>
<td>R 10 mg</td>
<td>31.2</td>
</tr>
<tr>
<td>pH 4.5</td>
<td>R 5 mg</td>
<td>49.8</td>
</tr>
<tr>
<td></td>
<td>R 10 mg</td>
<td>36.7</td>
</tr>
<tr>
<td>pH 6.8</td>
<td>R 5 mg</td>
<td>42.8</td>
</tr>
<tr>
<td></td>
<td>R 10 mg</td>
<td>33.9</td>
</tr>
</tbody>
</table>

Dissolution conditions: 900 mL, 100 rpm, baskets, 12 units tested

Comparative dissolution of R, 10/5/2.5 mg, pH 1.2

Similarity could not be demonstrated across the strengths of the reference product!!
CASE STUDY 2: cont.

The proposed approach: Testing at the same dose

2.5 mg T versus ½ 5 mg R
2x2.5 mg T versus 5 mg R

Sept 26-27th 2019, BioBridges, Prague
CASE STUDY 3: Metoprolol tartrate

European reference product: Seloken 100 mg
- lower strengths unavailable
- options for the authorization of lower strengths if similarity based on the strength-biowaiver cannot be demonstrated?

Metoprolol:
• Highly permeable compound
• Absorption > 95%
• $t_{\text{max}}$ 1.5–2 h
• BE demonstrated for tablets with different release characteristics
• dissolution not the rate-limiting
• range of dissolution profiles can be expected to yield equivalent plasma profiles


Figure 1. Mean dissolution profiles for metoprolol tartrate tablets used in biostudy.
CASE STUDY 3: cont.

The extension of guidance criteria for certain compounds?

Polli et al. (1997): Dissolution specification for metoprolol tartrate may be widened to “complete release in 60–90 min” and still assure BE
In Conclusion...

Keeping the rules is not comfortable in every situation!

Let’s make finding the new ways possible...
Acknowledgements:

Dr. Vít Perlík

Dr. Jiří Hofmann
Thank You For Your Attention