BCS-Based Biowaivers: Which Drugs are Eligible?

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Scope

- Biowaiver concept

- Application of the biowaiver procedure as a surrogate for bioequivalence testing
What is bioequivalence?

Therapeutic equivalence = Pharmaceutical equivalence + Bioequivalence
Bioequivalence study

Situations where regulatory authorities have to decide whether bioequivalence study is mandatory or not

- **within the product**
  - Scale up processes or variations after marketing authorization (Scale up and Post Approval Changes – US FDA and Variations - EMA)
  - Approval of lower dose products

- **with another product**
  - Approval of generics without clinical data
Bioequivalence study

Bioequivalence between the comparator and the test products can be demonstrated by any one of the following techniques

- Pharmacokinetic studies
- Pharmacodynamic studies (e.g. topical products for local use)
- Clinical trials
- Biowaiver procedure (based on BCS classification)
What is a Biowaiver?

“Biowaiver” means avoiding time consuming and costly pharmacokinetic studies and using *in vitro* dissolution test as a surrogate test to evaluate the bioequivalence of a test and reference product.

**Advantages**

- Circumvent expensive and sometimes unethically questionable human testing
- Reducing time in bringing product to the market
- Reduce product cost
BCS-Classification

Biowaiver approval is based on the Biopharmaceutics Classification System (BCS)

(1995 Amidon et.al)

If the *in vivo* dissolution of a highly soluble compound is *rapid* and *excipients* used in the product *do not affect absorption* of the API then bioequivalence between the two pharmaceutically equivalent IR products *need not be demonstrated using in vivo studies*. 
Timeline for evolution of biowaiver guidances

1995: SUPAC Guidances

2000: BCS based Biowaiver Guidance for Immediate Release Dosage Forms

2001: Note for Guidance on the Investigation of Bioavailability and Bioequivalence (Variations)

2003: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products

2006: Biowaiver Guidance Annex 8 TRS 937

2010: Guideline on Investigation of Bioequivalence

2011: General notes on BCS based biowaiver applications (PQP Guidance document)

201?: Updates in progress to FDA biowaiver document..
Applicable dosage forms

BCS based biowaivers are

applicable to

immediate release, solid pharmaceutical products for oral administration and

systemic action having the same pharmaceutical form

Not applicable to

sublingual, buccal and modified release formulations
Biowaiver procedure

**STEP 1**
Initial characterization and Determination of BCS Class of the API

- Aqueous solubility in GI pHs
- Permeability of the API

**STEP 2**
Risk Benefit Assessment

- Effect of excipients & manufacturing variables on BE, BA/BE problems unrelated to dissolution
- NTI, presence of "critical excipients", false positive biowaiver decision

**STEP 3**
Dissolution Characteristics of Comparator and Generic Products

- pure API, comparator and test products in pHs 1.2, 4.5 and 6.8
BCS-based solubility

**Highly soluble**

Dose/Solubility ratio ≤ 250mL in aqueous buffers
pHs 1 – 6.8 (7.5) at 37 ± 1°C

Dose is defined differently in different guidances

- **WHO**- highest dose strength mentioned in the EML
- **US FDA** – maximum dose strength that is marketed
- **EMA**- highest single dose that is administered

<table>
<thead>
<tr>
<th>Medium</th>
<th>pH</th>
<th>D/S Ratio (mL) D=153mg base</th>
<th>D/S Ratio (mL) D=600mg base</th>
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<tbody>
<tr>
<td>Water</td>
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<td>*SGF&lt;sub&gt;sp&lt;/sub&gt;</td>
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<td>246.85</td>
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<td>$SIF&lt;sub&gt;sp&lt;/sub&gt;</td>
<td>7.5</td>
<td>9243</td>
<td>-</td>
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</table>

Dose solubility ratios for amodiaquine hydrochloride in aqueous buffer at 37 °C
Permeability

Highly permeable

APIs with a permeability of $\geq 85\% \ (\geq 90\%)$ of the administered dose are defined as highly permeable.

Primary data (in humans)
- Absolute bioavailability
- Mass balance studies
- Intestinal perfusion studies

Secondary data
- Perfusion studies in animals
- *In vitro* permeability studies using CaCo-2 or MDCK cell lines along with reference substances
## Comparison between Guidances: BCS Class

<table>
<thead>
<tr>
<th>Class eligible for a biowaiver</th>
<th>Biowaiver guidances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FDA</td>
</tr>
<tr>
<td>I</td>
<td></td>
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<tr>
<td>II</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
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<tr>
<td>IV</td>
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</tbody>
</table>
Rickety turf

- Different derivatives of the API in test and comparator (salts that exhibit different solubility characteristics)

- Different polymorphs in test and comparator

- Poorly soluble drugs (most Class II and Class IV API)

- Reports of bioinequivalence not related to dissolution
  E.g. quinine sulfate

APIs with Narrow therapeutic index (NTIs) are a “NO GO” for biowaiver approach
Risk assessment

For the purpose of biowaiver “risk” can be defined as a “false positive” decision and the ramifications of such a product on patient safety.
Effect of formulation and manufacturing variable

Effect of excipients

Excipients that might affect bioavailability through non-dissolution mechanisms should be identified

e.g. sorbitol, mannitol, SLS and other surfactants.

Their impact on

- GI motility,
- susceptibility to interactions with the drug substance,
- drug permeability and
- interactions with membrane transporters should be discussed.

These excipients should preferably be qualitatively and quantitatively the same as in the reference product.
Risk benefit analysis

The risk associated with a „false positive“ biowaiver decision should be considered.

Bioavailability related issues like

- Previous cases of bioinequivalence reported that are not related to the dissolution
- Effect of supra or sub therapeutic drug levels in patients

The risk of a false biowaiver decision should not outweigh the benefits of a biowaiver procedure
**Dissolution test conditions**

**Apparatus:** Paddle or Basket

**N:** 12

**Volume of the medium:** 900mL or less

**Temperature of the medium:** 37±1°C

**Agitation speed:**
- 75rpm (paddle) → WHO
- 50rpm (paddle) → FDA/EMA or
- 100rpm (basket)

**Sampling times:** eg. 10, 15, 20, 30, 45, 60 min

**Media:**
- SGFsp, pH 1.2
- Acetate buffer, pH 4.5
- SIFsp, pH 6.8

*(note: no surfactants)*
Dissolution of pure API and products

• The test and the comparator products should be subjected to exactly the same battery of BCS-conform dissolution tests.

• Subjecting the pure drug substance to the series of dissolution studies as for the comparator product is a good approach to understand the drug behavior with respect to dissolution.
  
  e.g. wetting problems or if particle size needs to be reduced.

• The test conditions for Class I and III (II) APIs are the same but the evaluation criteria differs.

• It should be noted that the standard quality control dissolution test are usually not relevant for the biowaiver procedure.
Dissolution Criteria for Biowaiver

**Very Rapidly Dissolving**
- >85% release in 15 min in pH 1.2, 4.5 and 6.8 at 37°C

**Rapidly Dissolving**
- >85% release in 30 min in pH 1.2, 4.5 and 6.8 at 37°C
  - $f_2 \geq 50$

**BCS Class II: Poorly Soluble and Highly Permeable (WHO only)**
- “rapidly dissolving” product i.e. > 85% drug dissolution in 30 min from both comparator and test product in aqueous buffer at pH 6.8 at 37°C
ISSUE

If the comparator cannot meet the dissolution test criteria, biowaiver based approval is not possible

Possibilities!!!!

Either locate an acceptable alternative (as comparator listed in various jurisdictions could differ) or demonstrate BE by *in vivo* studies.
Summary

• Biowaiver procedure is a surrogate method of evaluating bioequivalence of generic products
• Just by belonging to Class I/III and/or fulfilling dissolution criteria does not entitle a product eligibility for a biowaiver approval
• Biowaiver decision can be arrived upon after evaluating the biopharmaceutical and clinical properties of the drug and the product.
• NTIs are NOT biowaiverable
• If critical excipients are used, then explanation regarding their choice and amounts need to be given to the regulatory authorities
• the risk associated with a „false positive“ biowaiver must not outweigh the benefit of applying a biowaiver procedure
Useful links


Thank you for your attention
Back up

ACETYL SALICYLIC ACID

“Gastrointestinal Instability”
Acetylsalicylic acid
Category: Non steroidal anti-inflammatory
Single Dose: 300-1000mg
pKₐ: 3.5
Log P: 1.18
Therapeutic index: wide
Permeability: high
Risk assessment: minimal

Challenges
• Acetylsalicylic acid (ASA) is prone to pH dependent hydrolysis to salicylic acid
• Salicylic acid (SA) is an active metabolite and hence the relevance of conversion of SA for a biowaiver decision needs to be evaluated
  - Stability indicating dissolution experiments
  - Modified solubility experiments need to be performed
Solubility and Dissolution Results

The goal of the solubility experiments was to demonstrate

<table>
<thead>
<tr>
<th>Medium</th>
<th>Shaking time (min)</th>
<th>Final pH</th>
<th>Average amount (mg) dissolved in 250ml</th>
<th>Dose/solubility ratio Max. Dose: 1000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1N HCl, pH 1.0</td>
<td>45</td>
<td>1.1</td>
<td>1176</td>
<td>&lt;212.76</td>
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<tr>
<td>Phosphate buffer, pH 3.5</td>
<td>20</td>
<td>3.0</td>
<td>1251</td>
<td>&lt;199.84</td>
</tr>
<tr>
<td>Acetate buffer, pH 4.5</td>
<td>15</td>
<td>3.5</td>
<td>1655</td>
<td>&lt;151.05</td>
</tr>
<tr>
<td>Phosphate buffer, pH 6.8</td>
<td>15</td>
<td>3.6</td>
<td>1910</td>
<td>&lt;130.89</td>
</tr>
</tbody>
</table>

Dissolution studies on ASA tablets show that hydrolysis of ASA without enzymatic assistance is rather slow.

The dose solubility ratio of ASA calculated using solubility data estimated at 37°C. Buffer concentrations were 50mM.

SA contributions to solubility and dissolution from ASA formulations in the framework of the biowaiver can be considered negligible.