Federal Institute
for Drugs
and Medical Devices

BCS-based Biowaivers
Some Controversial Topics

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Disclaimer

The presentation reflects

the personal opinion of the author

and not necessarily the official policy of the agency.

Contents

1. Drug Substance Solubility
2. Drug Substance – Strength vs. Dose Solubility
3. Drug Substance Absorption
4. Examples
5. Open Issues

Terms and Definitions

- **Bioequivalence Study**
    - In vivo comparison using humans as ‚dissolution models‘
    - ‚Biological quality control‘
    - Comparative evaluation of the formulation effect

- **Bioequivalence ⇒ therapeutic equivalence**

Conceptually

- The BCS-based biowaiver is not a ‘biorelevant’ investigation but excludes risks that could lead to formulation-related differences (drug substance and product) in terms of bioavailability!

Applicability

- **Evaluation of drug Substance and drug Product**
  - Drug substance
    - therapeutic aspects
    - physicochemical aspects

  - Drug product
    - In-vitro dissolution

Drug Substance Solubility

- **High solubility**
  - The highest single dose is completely soluble in 250 ml of aqueous solution at pH 1 - 6.8 (37 °C)

- **Investigations in at least three buffers** (preferably pH 1.2, 4.6, 6.8 and at the **pka***; replicate determinations; control of pH)
- **<u>Cave</u>: Possible stability problems have to be considered**

*needed?

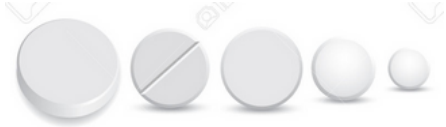
Drug Substance – Strength vs. Dose Solubility

Note:

- **Highest single dose** (EMA guideline and revised WHO guideline)

versus

- The **highest dose strength** (e.g. US-FDA)



Drug Substance – Strength vs. Dose Solubility

Pros - product strength vs. therapeutic dose:

- Straightforward and usually easy to be identified

Drug Substance – Strength vs. Dose Solubility

Cons - product strength vs. therapeutic dose:

- BCS classifications refer to drug substances, including specific salts, i.e. kind of superordinate (more general) characteristic, does not refer to formulations.
- Using the highest single dose ensures complete solubility of possible maximum dose as kind of 'worst-case-scenario'
- Product 'strength' is (not only but also) a matter of marketing strategy. As such it may vary over time and differ between products, e.g. capsules and tablets from the same MA holder.

Drug Substance – Strength vs. Dose Solubility

Cons - product strength vs. therapeutic dose (contd.):

- Ref. to product strength may lead to ‘strength-dependent‘ BCS classification/biowaiver (seems to be a contradiction in itself) with possibly strange implications, e.g. generics might apply for lower strengths only based on the BCS approach, but patients may use several units of such products in order to achieve the higher (now low soluble) dose

Drug Substance – Strength vs. Dose Solubility

Cons - product strength vs. therapeutic dose (contd.):

- Pediatric considerations may add another argument solubility class shift from I to II; (see AAPS Journal paper published by Shawahna, May 2016).
- Possible misclassification reg. permeability measurements as higher doses might saturate transporters

Drug Substance – Strength vs. Dose Solubility

Cons - product strength vs. therapeutic dose (contd.):

- Of note, retrospectively the relative risk for non-BE results is approximately four times lower for high solubility compounds as compared to low solubility compounds (namely BCS class 2) [Cristofoletti et al JPharmSci 2013]. In turn, this adds to the need to carefully/conservatively investigate and conclude on solubility according to the BCS.

Drug Substance – Strength vs. Dose Solubility

Dose vs Strength solution possible?

- Proposal to use PK-linearity to justify BCS-based BW of doses **above** the highest strength despite solubility limitations (*i.e.* highest strength does fulfill BCS BW criterion plus PK-linearity for AUC & Cmax over the dose range)
  - Criteria for linearity?
  - Reason(s) for non-linearity?

Drug Substance – Strength vs. Dose Solubility

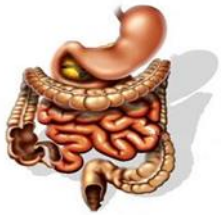
Dose vs Strength solution possible? (contd.)

- Including 'PK-linearity' entails the risk to employ the BCS-based BW for an amount of drug that is no longer (BCS) highly soluble.
- Including 'PK-linearity' introduces another source of variability/'uncertainty'

Permeability / Absorption

- **High permeability / absorption**
  - Ref. EMA guidance: “complete absorption” equals “extent of absorption is ≥ 85 %”
- **Assessment based on human data**
  - In-vitro data (e.g. Caco-2) may be supportive if valid

Permeability / Absorption



- **Human absorption data still preferred by EMA, however**
  - Caco-2 is quite advanced by now
  - Mass-balance results may stem from old literature and may be quite variable, i.e. hard to draw firm conclusions
  - (active) Transporter impact might be controlled by using the cell culture
  - Stability issues might be detectable by means of the cell culture

  - …….ongoing discussions expected

Example 1 – Concept of Risk Exclusion

- **"pH-dependent soluble, highly permeable, weak acidic, ionizable drug compounds may be handled like BCS class I drugs"** (e.g., chpt 8 in: Drug Bioavailability, van de Waterbeemd, Lennernäs, Artursson (edts) 2003 Wiley-VCH)
- **In vitro dissolution requirements acc. to previous WHO guidance**
  - at least 85% within 30 min at pH 6.8 and f2 testing for *pH 1.2 and 4.5* profiles *(note solubility?!)*
- Anyway no biowaiver for weak basic drugs!

JUSTIFIED?

- **Differences in rate of bioavailability (Cmax) were not detectable using this (theoretical) approach – hence, no longer accepted!**

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Example 2 – Concept of Risk Exclusion

- *ASS example: " The first objectionable issue is that, according to the data, the determination of solubility at pH 3.5 was terminated after 20 min, and the ones at pH 4.5 or 6.8, after 15 min, respectively, in order to limit the (scientifically proven) hydrolytic degradation to a convenient 2%. …"*

- Highest strength seems to be 500 mg in the US, but 800 mg in DE; highest single dose is 1000 mg (acc. to SmPC of Aspirin, Bayer, *i.e.* 2 tablets)

- **How to assign this as BCS 1 [Dressman et al J PharmSci 2012] and apply the BCS waiver?**

Example 3 – Concept of Risk Exclusion

- **Prodrugs – could be a matter of ‘instability’**

  Enalapril [Verbeek et al, accepted manuscript J Pharm Sci]

- (Dimethylfumarate (DMF) has been assigned BCS class 1 although DMF concentrations have never been detected)

- It is difficult to justify BCS classification for a compound already in the system due to biotransformation as respective BCS criteria cannot be applied.

Still under discussion

- **Divergent opinions on e.g.…**

- ….dose vs strength for solubility investigations
- ….the use/relevance of Caco-2
- ….the flexibility of *in-vitro* dissolution (e.g. agitation, and resulting specifications - what are appropriate dissolution specifications in case of a product approved with BCS class3 requirements (at least 85 % within 15 min))?
- ….the definition of instability

Thank you very much for your attention!

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