Federal Institute
for Drugs
and Medical Devices

Guideline in Development on (BCS)-Based Biowaivers ICH – M09: an Overview

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Disclaimer

The presentation reflects

the personal opinion of the author

and not necessarily the official policy of the agency.

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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

- **Evaluation of drug Substance and drug Product**
  - Drug substance
    - therapeutic aspects
    - physicochemical aspects
  - Drug product
    - In-vitro dissolution

Conceptually

- **The BCS-based biowaiver**

  - Does not have to meet acceptance criteria as with *in-vivo* BE
  - Represents kind of "**black&white**" BE surrogate which may be sometimes over-discriminating
  - Aim to exclude risks that could lead to formulation-related differences (drug substance and product) in terms of bioavailability, **but** is **not** a 'bio-relevant' investigation!

Current Status

- **Some Bioequivalence/BCS-based biowaiver guidelines**
  - ***EU***: Guideline on the investigation of bioequivalence, Appendix III (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **; 2010)
  - ***US***: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate- Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (new draft Guidance for Industry 2017)
  - ***Japan***: Guideline for Bioequivalence Studies of Generic Products (2012) ****
  - ***Canada***: Guidance Document: Biopharmaceutics Classification System Based Biowaiver (2014)
  - ***WHO***: Technical Report Series 992.WHO Expert Committee on Specifications for Pharmaceutical Preparations, 49th report, Annex 7

Current Status

- **US-FDA / EMA / 'others' / WHO**
  - General applicability including BCS class 1 and 3
  - pH range 1.2 – 6.8
  - Cut-off for extent of absorption ≥ 85 %
  - Generally ‚comparable' experimental conditions for *in-vitro* comparison

Current Status (contd.)

- **PMDA**
  - Personal communication from a PMDA colleague, some years ago: The concept of BCS-based biowaivers is <u>in principle</u> implemented:

    „BE of most IR products will be assured by the multimedia dissolution test used in Japan“?

  - However, no formal BCS based biowaiver for generics at the time being.

Drug Substance Solubility

- **High solubility** (as in many regions incl. EMA)
  - 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**
- Is there a need to discuss the type of buffer? [Bou-Chacra et al., The AAPS J, 19 (2017) 989]

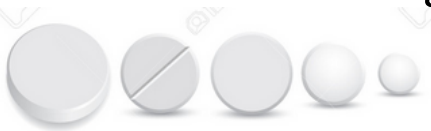
Drug Substance – Strength vs. Dose Solubility (1/8)

Note:

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

versus

- The **highest dose strength** (US-FDA and some other regions)



Drug Substance – Strength vs. Dose Solubility (2/8)

- ***FDA Guidance*** recommends for highest strength assessment with considerations for highest dose. ICH document prefers highest dose and then strength.
  - Sensitivity of highest strength studies on formulation effects
  - Relative BA or BE studies typically on highest strength

- FDA-internal assessment of previous FDA BCS-based applications tends to indicate *minimal impact* of dose vs strength
- Additional data/information (e.g. PK linearity) generally desired in borderline cases

Drug Substance – Strength vs. Dose Solubility (3/8)

Some Pros for using the highest therapeutic dose for BCS classification:

- BCS classifications refer to drug substances, including specific salts, *i.e.* it represents a superordinate (basic) characteristic irrespective of products market availability.
- 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 (4/8)

<u>Some Pros for using the highest therapeutic dose for BCS classification</u> (contd.):

- Ref. to product strength may lead to ‘strength-dependent‘ BCS 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 (5/8)

Some Pros for using the highest therapeutic dose for BCS classification (contd.):

- Current proposal to include 'PK-linearity' (though carefully worded) entails the risk to employ the BCS-based BW for an amount of drug that is no longer highly soluble.
- Including 'PK-linearity' will introduce another source of variability/'uncertainty' due to the 'definition' of linearity itself.

Drug Substance – Strength vs. Dose Solubility (6/8)

example - product strength vs. therapeutic dose:

- Torasemide
  - Different polymorphs with different solubility
  - pH dependent solubility (low at pH 5)
  - Permeability looks like not critical (though variable)

Drug Substance – Strength vs. Dose Solubility (7/8)

example - product strength vs. therapeutic dose:

- Torasemide (contd.):
  - Lit. [JPP 2006, 58:1475] : *"Torasemide has been classified as a Class I drug according to the BCS up to a maximum dose of 40 mg….."*
  - Lit. [AAPS J 2017, 19:989] : *"…torasemide, a Class I drug according to the BCS, ….."*
  - Highest dose in the US seems to be 100 mg
  - Highest dose in the EU seems to be 200 mg according to the SmPC

Drug Substance – Strength vs. Dose Solubility (8/8)

example - product strength vs. therapeutic dose:

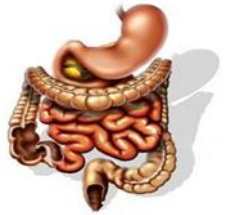
- Torasemide (contd.):
  - PK linearity can be perfectly demonstrated between 2.5 and 200 mg for both AUC and Cmax
  - *In-vitro* dissolution results at pH 5 (50 rpm!) only indicate the difference that can be detected *in-vivo*, i.e. confidence interval not within usual acceptance criteria for Cmax.
- How flexible should the BCS be applied?! Does PK linearity really allow to apply the BCS-based biowaiver for drugs with limited solubility?

Permeability / Absorption (1/2)

- **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 (2/2)

- **EMA guidance: absorption currently preferred because**
  - Limitations of Caco-2 like e.g.:
    - No transporters
    - No mucus
    - Differences reg. tight junctions
  - However, risk of misclassification (i.e. false positive BCS class 1) seems rather limited if Caco-2 is correctly used.



Harmonisation reg. assessment / evaluation of excipients

- **FDA**
  - Application of SUPAC, Q1/Q2, aso
- **EMA**
  - Use of less and more critical excipients, qualitative and quantitative sameness and/or similarity, aso

- Struggle to find reasonably justified **cut-offs** rather than talking about ‘very similar’ or ‘large quantities’

Harmonisation possible reg. assessment / evaluation of excipients (contd.)

- **Current ICH approach…**
  - …includes definite **cut-off** values
  - …is going to differentiate between '**critical**' and '**other**' excipients
  - …hoping for data-based comments including 'failed' studies, as the latter are hardly available

Dissolution aspects for harmonization

- **Regarding experimental conditions**
  - Which volume is most reasonable and/or relevant for comparative in-vitro dissolution experiments?

    (see latest US-FDA BCS draft guidance publ. in Dec 2017)

Dissolution aspects for final harmonization

- **Regarding experimental conditions**

- FDA Guidance recommends 500 ml as preferred volume (and 900ml where *justified*), and 75 rpm paddle speed with '*justification*'

- ICH document prefers 900 mL (or less with *justification*) and 50 rpm only

- Additional data may be provided by FDA/other sources in the future for ICH purposes

Dissolution aspects for final harmonization

- **Regarding experimental conditions (contd.)**
  - Some regions do not support increasing **agitation** beyond 50 rpm – can this be addressed by switching from paddle to basket?
  - How to address '**coning**' correctly and scientifically sound?
  - **Water** implemented as additional 'low buffer capacity' medium as found in Japanese guidances

- **Note: Specifications should reasonably fit!**

Additional aspects for final harmonization

- **Further issues:**

  - Applicability of the BCS-based biowaiver for pro-drugs which are bio-transformed prior to absorption? The issue of ‘(in)stability’ has been implemented!
  - Applying the BCS-based biowaiver approach for different salts and pharmaceutical alternatives has been deleted which would be a new restriction for the EU!

Just as examples

- **Prodrugs – could be a matter of ‘instability’**
  - Capecitabine (see product-specific guidance from US FDA and EMA)
  - Dimethylfumarate has been assigned BCS class 1 although its concentrations have never been detected in plasma
    - It is difficult to justify BCS classification for a compound already in the system due to biotransformation as respective criteria cannot be applied

… best possible ‘risk assessment’…

- **…by means of BCS-based Biowaiver in order to minimize (if not exclude)**
  - possible product differences regarding
    - „… the physical-chemical principles that govern the preparation and behavior of the medicinal agent or drug product.“ *
  - The BCS-based Biowaiver represents a rather simplified equivalence concept that works only based on particular prerequisites

* acc. to. Biopharmaceutics Applications in Drug Development R. Krishna and L. Yu edt.; Springer

Special Thanks to….

- **…all colleagues from the ICH-M9 working group!!**

Thank you very much for your attention!

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