Federal Institute
for Drugs
and Medical Devices

BCS-Based Biowaiver Guideline ICH – M09 Comments

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Disclaimer

The presentation reflects

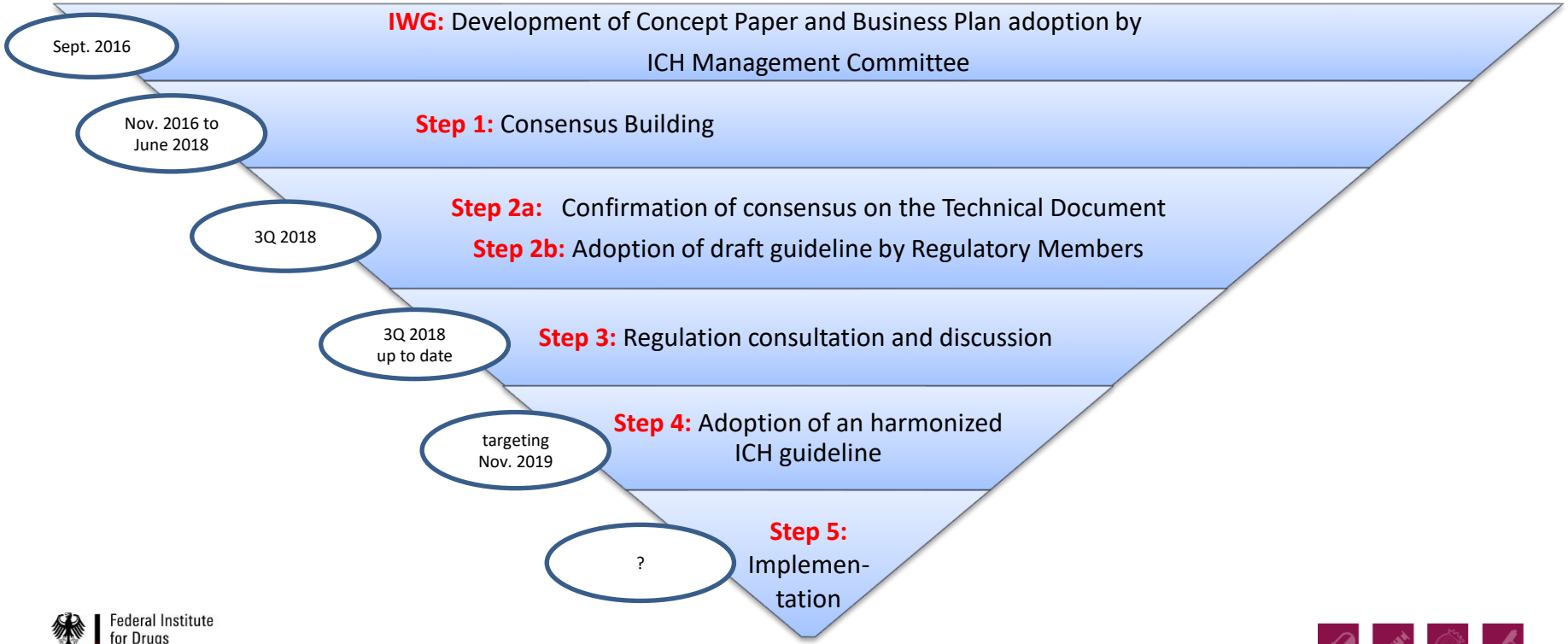
the personal opinion of the author

and not necessarily the official policy of the agency.

Contents

1. Timeline of Activities for ICH M09
2. Conceptual Misunderstanding?
3. Solubility
4. Permeability
5. Excipients
6. *In-vitro* Dissolution
7. Concluding Thoughts

Timeline of Activities for ICH M09



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Conceptual Misunderstanding? Pro-Drugs vs Metabolite

- **Pro-drugs vs metabolite – how to classify**
  - Meaning of BCS classification
  - Link between drug substance and product

Conceptual Misunderstanding?
Case Study Example

- **Case study example**
  "It is very difficult to uniquely and unambiguously assign a Biopharmaceutical Classification System (BCS) classification for a pro-drug. The pro-drug (XY) is BCS class III, but it is rapidly converted into the drug (ZZ) by pre-systemic brush border metabolism and there are no reports of circulating levels of XY. ZZ is therefore classified as a BCS class I compound and due to the rapid metabolic clearance, XY can therefore be tentatively classified as a BCS class I/III compound."

?

Conceptual Misunderstanding?
Handling of ODTs

- **Handling of ODTs – Why to consider intake with water?**
  - Definition of BCS solubility
  - Meaning of multimedia testing vs GI transit and site of ‘transport’ vs the general intention to develop an ODT ☺

Conceptual Misunderstanding?
NTI Drugs

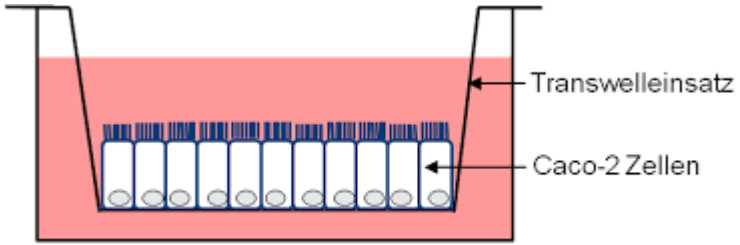
- **NTI drugs**
  - Meaning of narrowed BE acceptance limits vs…
  - ….BCS based biowaiver product comparison…

Solubility

- **Experimental uncertainty**
  - How extensive
  - Handling of variability
  - Equilibrium solubility may not be required

Permeability

- **‘In-vitro/non-human’ experiments**
  - Other cell lines than Caco-2
  - Too many ‘model’ drugs for validation purposes

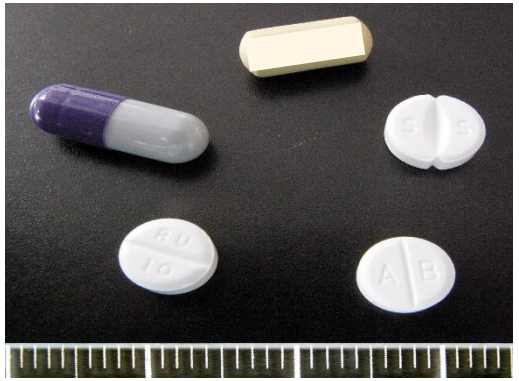


Excipients

- **Similarity of excipients in test and reference products**
  - Cut-off values too strict or too flexible?
  - Reversed engineering possible?
  - Definition of ‘critical’ excipients?
  - Possibility to “justify” deviation from requirements?

In-vitro Dissolution

- **Meaningfulness of multimedia *in-vitro* investigations**
  - Use of f2 or other methods
  - Handling of variability
  - ‘Coning’ and agitation
  - Waiver of strengths based on a BCS-based biowaiver



In-vitro Dissolution cont'd

- **Gentle reminder – the BCS based biowaiver dissolution…**
  - …is kind of worst case investigation
  - …is nothing about discriminatory experimental methods
  - …is not using biorelevant methods
  - …is for excluding risks based on ***pre***-requisites

Particular Comments

- **“….the ICH M09 guideline appears very strict leaving almost no space for case-by-case justification…”** ☺
  - The framework should be clear
  - Misuse of the concept will likely ‘kill’ it as it constitutes an *in-vivo* surrogate
  - Where to draw the line for so-called case-by-case decisions
  - Still quite some assumptions in the concept

… 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

… concluding thoughts

- **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!

AGAIN - Special Thanks to….

- **…all colleagues from the ICH-M09 working group!**

Thank you very much for your attention!

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