Permeability studies from an innovator perspective for BCS biowaiver support

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M-CERSI workshop: Drug Permeability: Best Practices for BCS-based Biowaivers
Agenda

• Role of Permeability in drug development
  • Why it's important
  • Example of where/when and how it is assessed
• ICH M9
  • Benefits
• Opportunities (wish list 😊)
• Conclusions
Permeability Assessment’s Role in Drug Development

Permeability: It’s not just for BCS Classification!

1997 Epiphany! – Most compounds need to reach the systemic circulation in order to “work”

Lipinski’s Rule of 5

- Orally active compounds
- Four physicochemical parameter ranges were associated with 90% of orally active drugs that have achieved phase II clinical status.
- These factors are correlated with adequate absorption through a substance’s aqueous solubility and intestinal permeability

Industry reacted quickly - By 2000, PK/bioavailability no longer the major reason for attrition


Preclinical Assessment

Historically

Initial – Low through put (rat intestinal perfusion)

Now – High through put screens

- Cell line assays: Caco-2, MDCKII, PAMPA, etc.


Permeability in Drug Development

- High throughput permeability assessment
- Predictive
- For Development: Development decisions (yes/no)

- Individual compound
- Predictive
- For “regulatory”: Pathway decisions (for BE)
Preclinical Permeability Assessment

A current practice

- Caco-2 may not be the method of choice (e.g. MDCK-LE)

| P<sub>e</sub><sub>app</sub> at Donor pH 6.5 and Receiver pH 7.4 (x10<sup>-6</sup> cm/s) |
|--------------------------|--------------------------|
| 0                        | 100                      |
| 20                       | 80                       |
| 30                       | 60                       |
| 40                       | 40                       |
| 50                       | 20                       |
| 60                       |                           |

- Rationale

  - Comparable and in some cases superior ability to accurately determine permeability versus other cell lines such as MDCKII-WT and Caco-2
  - MDCKII-LE cell line is very robust, cost-effective, and easy to work with (compared with Caco-2)
  - Offers clear benefits over MDCKII-WT with less background transporter signals and less probability of interference.

Methods for BCS classification suitable for regulatory submissions

A current practice

- Urinary Excretion from FIH
  - Pro: Human data – “built in” to studies already
  - Con: Very few compounds are excreted ≥ 85% unchanged in urine

- Mass balance/micotracer study
  - Pro: Human data universally acceptable
  - Con: Capacity (need for synthesis of radiolabeled compound for study)

- Caco-2
  - Pro: Acceptable via ICH
  - Con: Caco-2 assessment and supporting studies needed (e.g. stability, etc.) and not part of standard development.
Permeability Classification via Mass Balance Study

Use of microtracer doses allows calculation of absolute bioavailability and fraction absorbed

Figure 1 Study design. $T_{\text{max}}$ time to maximum concentration.
M9 Biopharmaceutics Classification System-Based Biowaivers
Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-343-3744 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/Drugsafety-Compliance-Enforcement/Information/insances/drugs
and/or
Office of Communication, Outreach and Development
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Food and Drug Administration
10903 New Hampshire Ave., Bldg. 31, Room 3128
Silver Spring, MD 20993-0002
Phone: 301-435-4709 or 246-002-8010
Email: occid@fda.hhs.gov
https://www.fda.gov/Drugs/Drugsafety-Compliance-Enforcement/Information/biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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ICH
ICH is Important!

• Establishes a “best practice” for industry to follow

• Eliminates “regulatory uncertainty”

• Avoids practice being set by most conservative agency
  • E.g., if one regulatory agency requires clinical BE study and the others don’t, the practice will be to conduct the clinical BE study.

• So for all who worked on ICH M9 – THANK YOU!
Permeability: ICH M9 - Advances:

• Benefits
  • Lowered highly permeable limit from 90 to 85% (more compounds qualify)
  • Caco-2 now “routinely” accepted
  • More countries accept biowaivers

Criteria and support of permeability:
• A drug substance is considered highly permeable if ≥ 85% of the administered dose is absorbed.
• A conclusion of high permeability may be supported by:
  • an absolute bioavailability ≥ 85%;
  • ≥ 85% of the administered dose recovered in urine and/or feces as absorbed drug material;
  • results of validated *in vitro* Caco-2 permeability assays.
And ... it is nearing Christmas
And ... I think I have been very good, so ... for consideration
ICH M9 Guideline in Development on Biopharmaceutics
Classification System-Based Biowaivers: An Industrial Perspective
from the IQ Consortium

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Wish list comes from:

**ABSTRACT:** In October 2016, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) ICH began efforts to provide recommendations to harmonise guidelines for biopharmaceutics classification system (BCS)-based biowaivers. Topics to be addressed included consideration of the dose used to classify solubility, tests, and criteria for establishing highly permeable, dissolution conditions, the influence of excipients, and aspects of product strength. The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) is a technically focused organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators, and the broader R&D community. Its members have substantial expertise in all scientific domains associated with BCS-based waivers and drug product quality, as well as considerable experience in the application of BCS-based biowaivers. The ICH process recognizes that harmonization is achieved through the development of guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side. Thus, to facilitate these efforts and to encourage open and transparent discussion of other perspectives that may exist, IQ offers their perspective on these and related topics.

**KEYWORDS:** biopharmaceutics classification system (BCS), bioequivalence (BE), biowaivers, permeability, solubility, dissolution, regulatory
Wish 1: Consider expanding acceptable methods by establishing validation criteria

If validation criteria are met, method would be considered acceptable

There are numerous methods/cell lines that maybe as good or better than Caco-2*

- Cell lines: MDCK (MDCK-LE), HT29, TC7, and 2/4/A1, primary human intestinal cells, Induced pluripotent cells
- Co-cultures: Caco-2/HT29-MTX cells, Caco-2/HT29-MTX/Raji B cells, Caco-2 cells/Hepatocytes
- Assay systems: Co-cultures, 3-D cultures, microfluidic systems

Benefits

- Somewhat precedent: Similar to ICH M9 Annex 1-
  Caco-2 Cell Permeability Assay Method Considerations
- Allows a way to keep up with the science without necessarily having to restart the ICH process

Wish 2: State that a totality-of-evidence approach is acceptable

**Approach**

- When a single method fails to demonstrate a permeability classification conclusively, two or more different methods would be allowed, and permeability classification based on the totality of the available data. In this context, data from other animal or cellular studies may provide strong supportive evidence sufficient to demonstrate a permeability classification.

- It is important to note that if there is conflicting information, it is important to note that human data supersede in vitro and animal data. For example, there are cases where compounds have been identified as substrates for efflux transporters, yet the fraction absorbed is more than 90% across the therapeutic range of doses.

**Rationale**

- While some agencies always open to this approach, others are “more conservative” resulting in defaulting to clinical BE trials.
  - It is always preferable to establish BE adequately without a clinical BE trial
    - Healthy volunteers receive no direct benefit from participating – there is only potential risk.
  - This should result in all agencies considering the approach
    - It is recognized that it will still be “a review issue”.

Wish 3 – Full implementation

From the ICH website and regulatory agency websites

<table>
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<tr>
<th>Implementation status:</th>
<th>Comment</th>
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<tr>
<td>ANVISA, Brazil - In the process of implementation; Date: 1 November 2029; Reference: RDC 37/2011</td>
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<td>EC, Europe - Implemented; Date: 30 July 2020; Reference: EMA/CHMP/ICH/493213/2018</td>
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<td>FDA, United States - Implemented; Date: 11 May 2021; Reference: Posted on FDA, United States website</td>
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<tr>
<td>TFDA, Chinese Taipei - Implemented; Date: 31 August 2016; Reference: BCS biowaiver guideline for Generics</td>
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Some have likely advanced to full implementation
Another Application for BCS Based Waivers? – Solution

From: M9: Biopharmaceutics Classification system-based Biowaivers Step 4 document – to be implemented Prepared by the ICH M9 Expert Working Group Date February 2020

Key Principles (continued)

• The BCS-based bio waiver is only applicable to immediate release, solid orally administered dosage forms or suspensions designed to deliver the drug to the systemic circulation.

Pediatric Formulation Development

• Pediatric formulation development often lags behind adult formulations

• It is not unusual to introduce a solution for pediatrics after the immediate release, solid oral formulation is on the market.

• If the solid oral formulation is a BCS Class 1 or 3 and rapid or very rapidly dissolving, consider when a BE study can be waived.

Rationale – Rapidly dissolving formulations of BCS Class 1 & 3 compounds act as solutions (GASP) – Asking folks to consider 2 different dosage forms
Conclusions

• Permeability is used for more than BCS classification
  • Important predictor of human PK

• It is typically assessed prior to first in human and then again during clinical development
  • Not always assessed in with methodology that is currently acceptable via ICH M9

• Opportunities to modify ICH M9 further:
  • Method qualification/validation criteria to allow new methodologies
  • Considerations for totality-of-evidence approach
  • Waiver for solution formulation of a BCS Class I solid oral formulation
Thank You!

Happy to take questions if there is time