CERSI
University of Maryland

Permeability studies from an innovator perspective for BCS biowaiver support

Jack Cook, Pfizer Inc.

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

December 6, 2021

Agenda

- Role of Permeability in drug development
  - Why its important
  - Example of where/when and how it is assessed
- ICH M9
  - Benefits
- Opportunities (wish list ☺)
- Conclusions

Permeability Assessment's Role in Drug Development

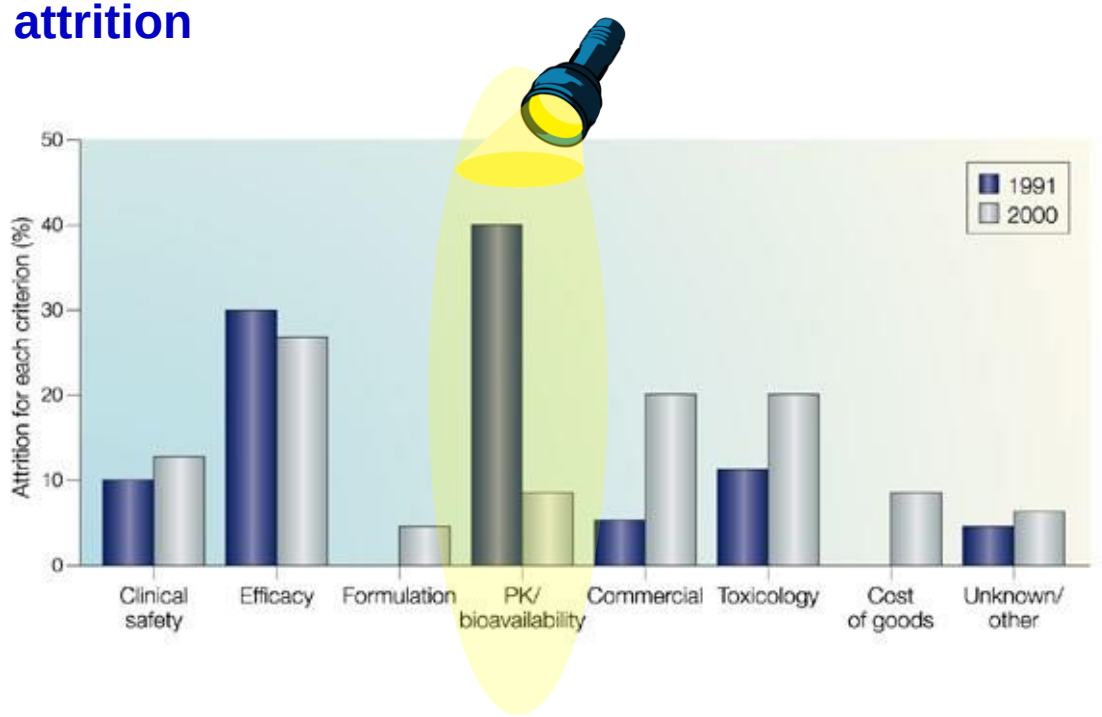
Permeability: It's not just for BCS Classification!

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



Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001 Mar 1;46(1-3):3-26. doi: 10.1016/s0169-409x(00)00129-0.

*Kola, I., Landis, J. Can the pharmaceutical industry reduce attrition rates?. Nat Rev Drug Discov 3, 711–716 (2004). https://doi.org/10.1038/nrd1470

Preclinical Assessment

Historically

Initial – Low through put (rat intestinal perfusion)

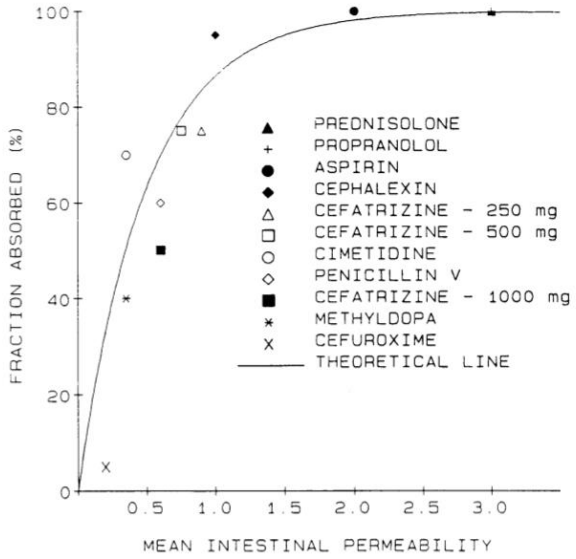


Fig. 1. Plot of the fraction dose absorbed (%) versus the mean dimensionless intestinal wall permeability. Wall permeabilities were calculated from steady-state rat intestinal perfusion experiments.

Amidon GL, Sinko PJ, Fleisher D. Estimating human oral fraction dose absorbed: a correlation using rat intestinal membrane permeability for passive and carrier-mediated compounds. Pharm Res. 1988 Oct;5(10):651-4. doi: 10.1023/a:1015927004752. PMID: 3244618.

Now – High through put screens

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

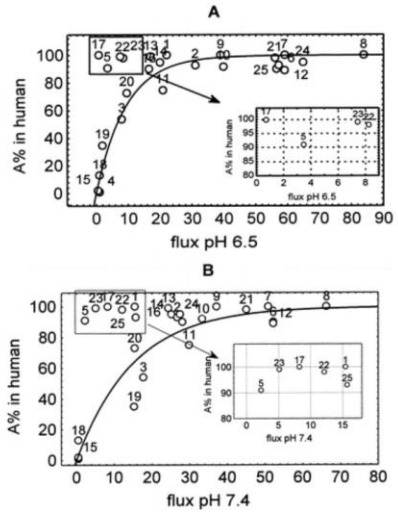
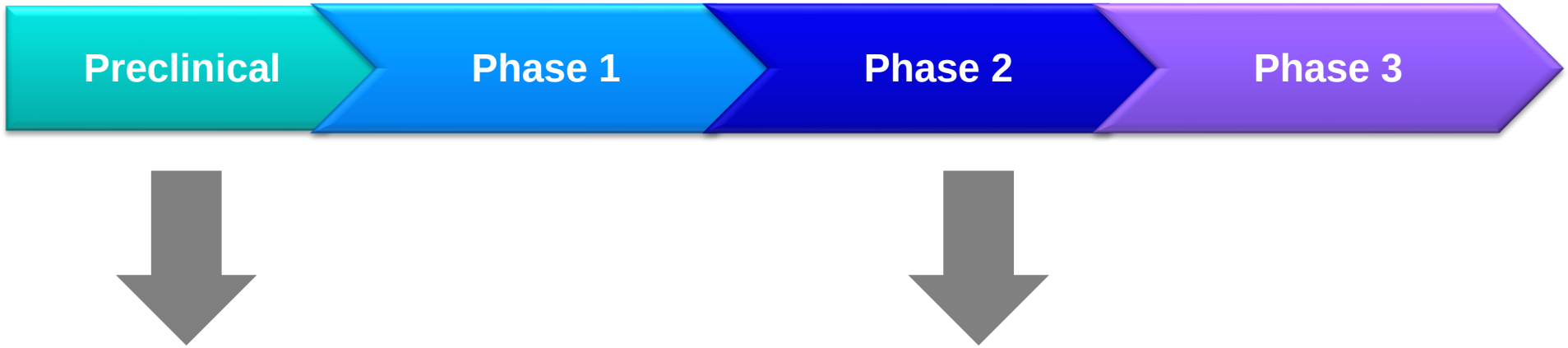


Figure 3 PAMPA flux at different pH values versus human absorption data (see Table 1 for measurement results). Insets describe compounds which are actively transported or polar compounds with low molecular weight, which can assumed to be absorbed by the paracellular route in human: (A) pH 6.5; (A) pH 7.4.

Manfred Kansy, Frank Senner, and Klaus Gubernator. Physicochemical High Throughput Screening: Parallel Artificial Membrane Permeation Assay in the Description of Passive Absorption Processes. Journal of Medicinal Chemistry 1998 41 (7), 1007-1010. DOI: 10.1021/jm970530e

Permeability in Drug Development



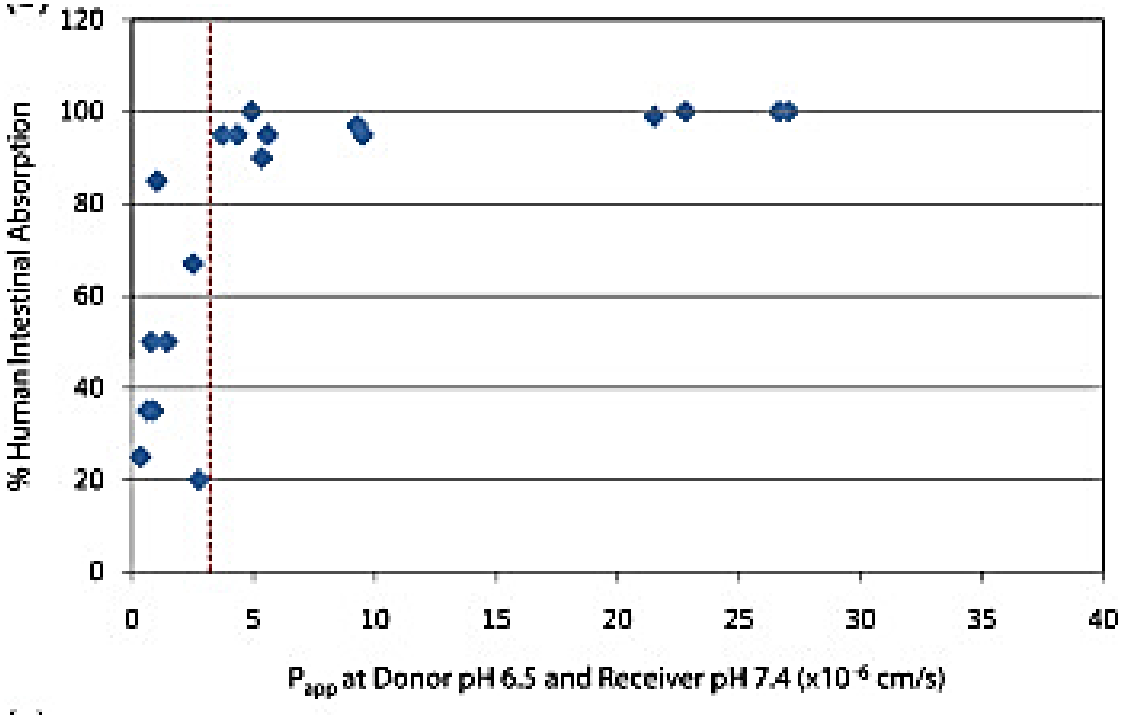
- High throughput permeability assessment
- Predictive
- For Development: Development decisions (yes/no)

- 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)**



- **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.

*Li Di, Carrie Whitney-Pickett, John P. Umland, Hui Zhang, Xun Zhang, David F. Gebhard, Yurong Lai, James J. Federico, Ralph E. Davidson, Russ Smith, Eric L. Reyner, Caroline Lee, Bo Feng, Charles Rotter, Manthena V. Varma, Sarah Kempshall, Katherine Fenner, Ayman F. El-kattan, Theodore E. Liston, Matthew D. Troutman, Development of a new permeability assay using low-efflux MDCKII cells, Journal of Pharmaceutical Sciences, Volume 100, Issue 11, 2011, Pages 4974-4985, https://doi.org/10.1002/jps.22674.

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

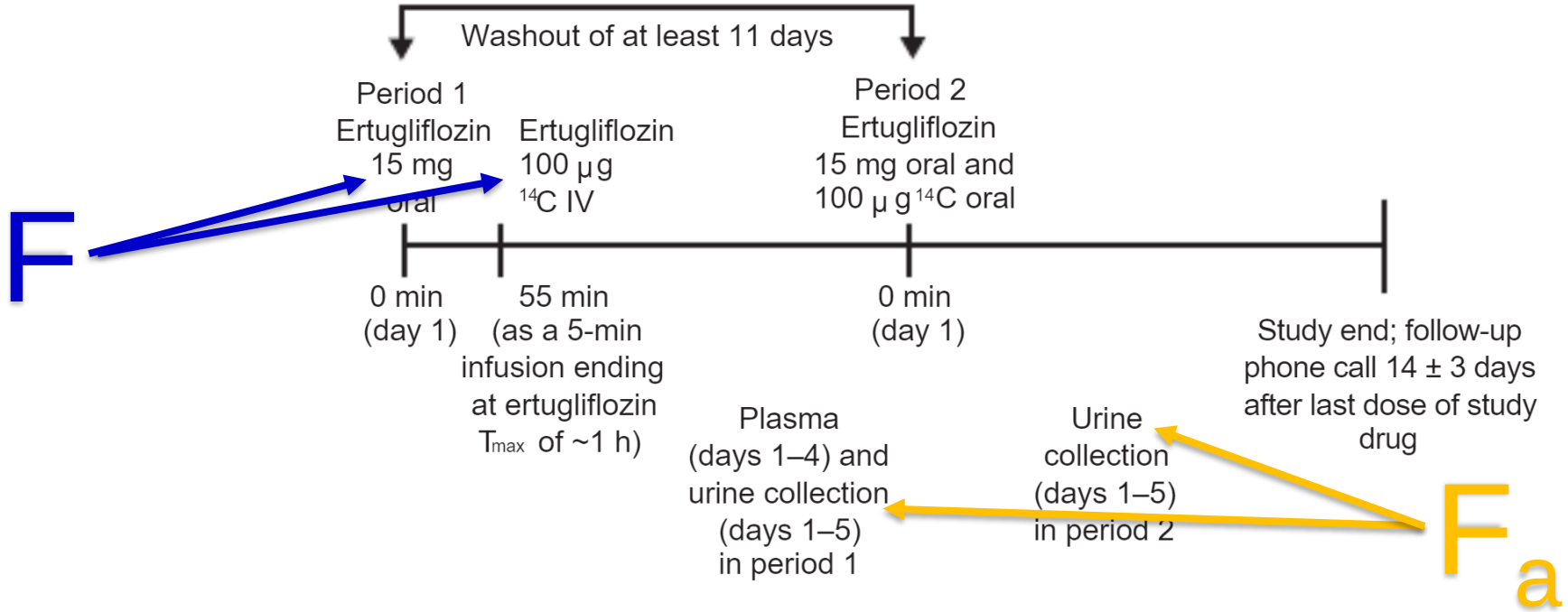


Figure 1 Study design. T_{max}, time to maximum concentration.

Raje, S., Callegari, E., Sahasrabudhe, V., Vaz, A., Shi, H., Fluhler, E., Woolf, E.J., Schildknegt, K., Matschke, K., Alvey, C., Zhou, S., Papadopoulos, D., Fountaine, R., Saur, D., Terra, S.G., Stevens, L., Gaunt, D. and Cutler, D.L. (2018), Novel Application of the Two-Period Microtracer Approach to Determine Absolute Oral Bioavailability and Fraction Absorbed of Ertugliflozin. Clinical And Translational Science, 11: 405-411. https://doi.org/10.1111/cts.12549

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: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-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)

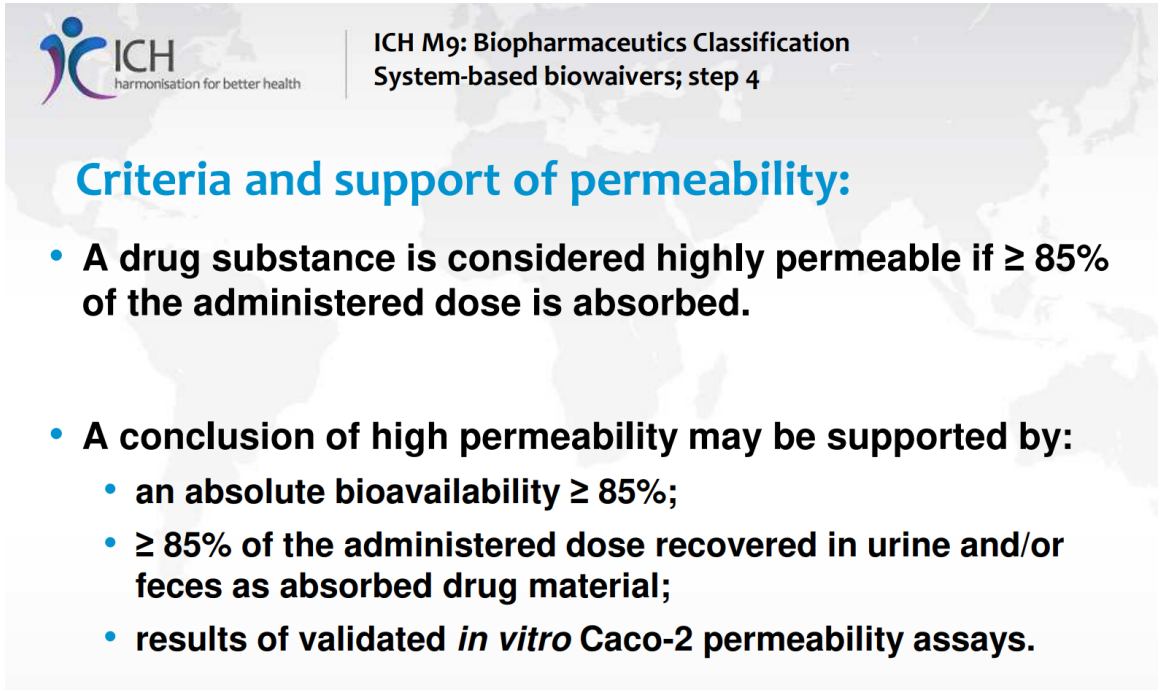
May 2021
ICH

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

And … it is nearing Christmas
And … I think I have been very good, so … for consideration

Wish list comes from:

molecular pharmaceutics

Perspective

Cite This: *Mol. Pharmaceutics* 2020, 17, 361−372

ICH M9 Guideline in Development on Biopharmaceutics Classification System-Based Biowaivers: An Industrial Perspective from the IQ Consortium

Philip Bransford,[†] Jack Cook,[*,‡] Manish Gupta,[§] Sebastian Haertter,[○] Handan He,[∥] Rob Ju,[⊥] Jitendra Kanodia,[▽] Hans Lennernäs,[¶] David Lindley,[#] James E. Polli,[◆] Larissa Wenning,[+] and Yunhui Wu[⊖]

[†]Vertex Pharmaceuticals Incorporated, 50 Northern Avenue, Boston, Massachusetts 02210, United States

[‡]Clinical Pharmacology Department, Global Product Development, Pfizer, Inc., Groton, Connecticut 06320, United States

[§]Biopharmaceutics, Product Development and Supply, GlaxoSmithKline, Collegeville, Pennsylvania 19426, United States

[○]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut 06877, United States

[∥]Department of Drug Metabolism and Pharmacokinetics, Novartis Institutes for Biomedical Research, East Hanover, New Jersey 07936, United States

[⊥]Drug Product Development, Abbvie, North Chicago, Illinois 60064, United States

[▽]Theravance Biopharma US, Inc., South San Francisco, California 94080, United States

[¶]Department of Pharmacy, Uppsala University, Box 580, 751 23 Uppsala, Sweden

[#]AbbVie Inc., North Chicago, Illinois 60064, United States

[◆]Department of Pharmaceutical Sciences, University of Maryland, Baltimore, Maryland 21201, United States

[+]Pharmacokinetics, Pharmacodynamics and Drug Metabolism, MRL, Merck & Co., Inc., West Point, Pennsylvania 19486, United States

[⊖]Pharmaceutical Sciences, MRL, Merck & Co., Inc., West Point, Pennsylvania 19486, United States

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 harmonize guidances 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.

Harmonization of Biopharmaceutics Classification System-based Biowaivers

KEYWORDS: *biopharmaceutics classification system (BCS), bioequivalence (BE), biowaiver, 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 precedented: 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

*Donna A. Volpe (2020) Advances in cell-based permeability assays to screen drugs for intestinal absorption, Expert Opinion on Drug Discovery, 15:5, 539-549, DOI: 10.1080/17460441.2020.1735347

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

Implementation status:

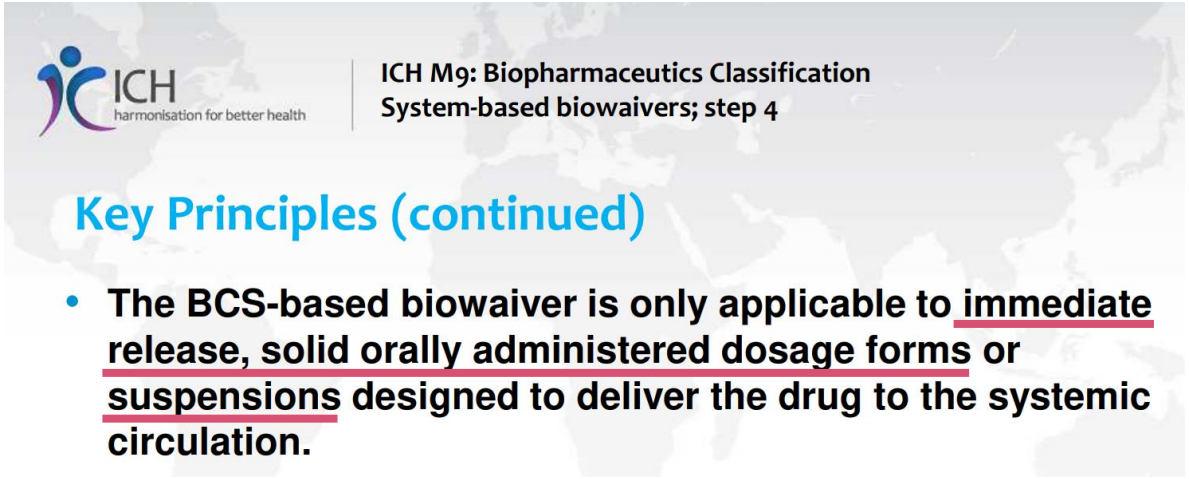
- **ANVISA, Brazil** - In the process of implementation; Date: 1 November 2029; Reference: RDC 37/2011
- **EC, Europe** - Implemented; Date: 30 July 2020; Reference: EMA/CHMP/ICH/493213/2018
- **FDA, United States** - Implemented; Date: 11 May 2021; Reference: Posted on FDA, United States website
- **HSA, Singapore** - In the process of implementation;
- **Health Canada, Canada** - Implemented; Date: 26 August 2020; Reference: File #: 20-109235-116
- **MFDS, Republic of Korea** - In the process of implementation; Date: 1 December 2021;
- **MHLW/PMDA, Japan** - Implemented; Date: 25 December 2020; Reference: PSEHB/PED Notification No. 1225-13
- **NMPA, China** - In the process of implementation; Date: 7 November 2021; Reference: NMPA, China Announcement No. 61 [2021]
- **Swissmedic, Switzerland** - Implemented; Date: 1 August 2020;
- **TFDA, Chinese Taipei** - Implemented; Date: 11 August 2016; Reference: BCS biowaiver guideline for Generics

Comment

- 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



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 predicter 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