BCS based Biowaiver
Assessment of Permeability

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Boehringer Ingelheim

Disclaimer

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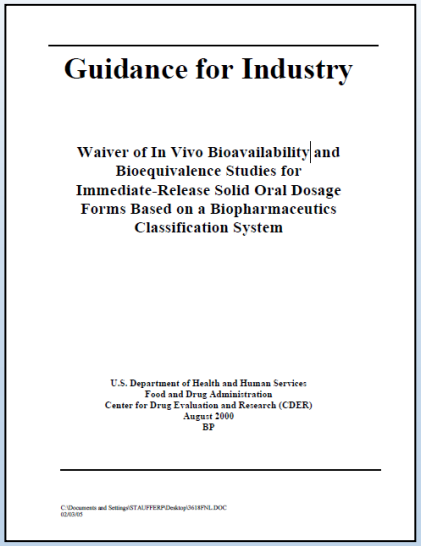
Start of ICH M09 in 2016

- **FDA**

- Classification based on solubility and **permeability**
- **Human PK or intestinal permeability methods**
- **Absorption ≥ 90 %**



Guidance for Industry

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2000
BP

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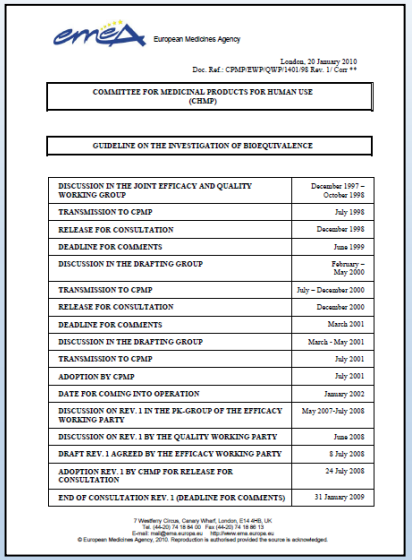
02/03/05

- **EMA**

- Classification based on solubility and **absorption**
- **Human PK or reliable literature data**
- **Absorption ≥ 85 %**



emea European Medicines Agency

London, 20 January 2010
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING GROUP	December 1997 – October 1998
TRANSMISSION TO CPMP	July 1998
RELEASE FOR CONSULTATION	December 1998
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DATE FOR COMING INTO OPERATION	January 2002
DISCUSSION ON REV. 1 IN THE PK-GROUP OF THE EFFICACY WORKING PARTY	May 2007-July 2008
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ADOPTION REV. 1 BY CHMP FOR RELEASE FOR CONSULTATION	24 July 2008
END OF CONSULTATION REV. 1 (DEADLINE FOR COMMENTS)	31 January 2009

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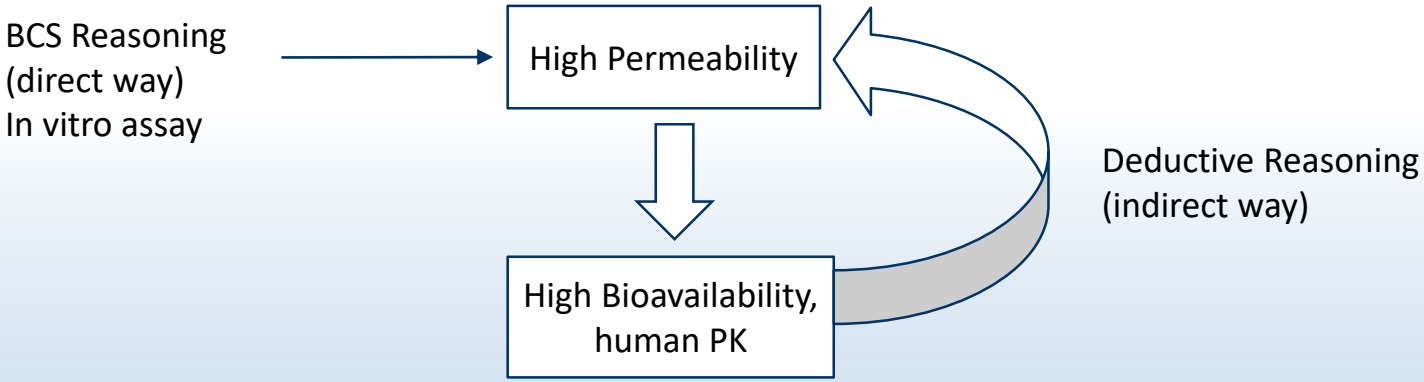
Adapted froim Bhoopathy, 2014

Why *in vivo* was predominant in the past

- Lack of confidence in in vitro system – definition of permeability via in vivo human PK parameter. Proof of the cause by the result



- **TRUE, no abs BA ≥ 85% without being highly permeable but highly permeable without abs BA ≥ 85% .**
- **Proof of BCS I, high permeability may be challenging for highly metabolized compounds – value of mass balance?**

mass balance as proof of permeability?

- Mass Balance studies usually with only few (< 10 subjects); sometimes high inter-individual variability
  - Urinary recovery of 29-63% and fecal recovery of 18-38%
  - Absorption range of 74-100% based on urine recovery
- Retrospective Analysis of 171 studies resulted in mean recovery of 89% (± 11%); 25% (42) < 85 % recovery! Low recovery related to long plasma radioactivity half-life (hence, most likely not permeability/absorption!)e.g. Fluoxetine: BCS I but only 80% total recovery!
- Major methodological issue with extractability from feces
  - The extractability of a certain metabolite can be especially difficult and is missed in the balance;
  - fecal elimination appears to be of greater importance for drugs that yield lower recovery values.

Roffey et al., 2007

mass balance as proof of permeability (Cont.)?

- poor balance in CYP2D6 extensive metabolizers (61%), yet good recovery in poor metabolizers (89%). Although counterintuitive (as one might expect more rapid metabolism to lead to more rapid excretion), CYP2D6 metabolism led to the formation of a long-lived metabolite that potentially covalently binds to macromolecules. (Roffey et al, 2007)
- Some metabolism difficult to discern between oxidative and reductive - N-demethylation such as Methamphetamin to Amphetamin. (Sousa et al., 2008)
- volatile metabolites (CO2) being missed
- Reductive metabolites formed by gut bacteria may be absorbed to a substantial amount - example deleobuvir, 15% of total radioactivity in plasma. (Chen et al., 2015) or even excreted into urine - example metronidazole. (Sousa et al., 2008)

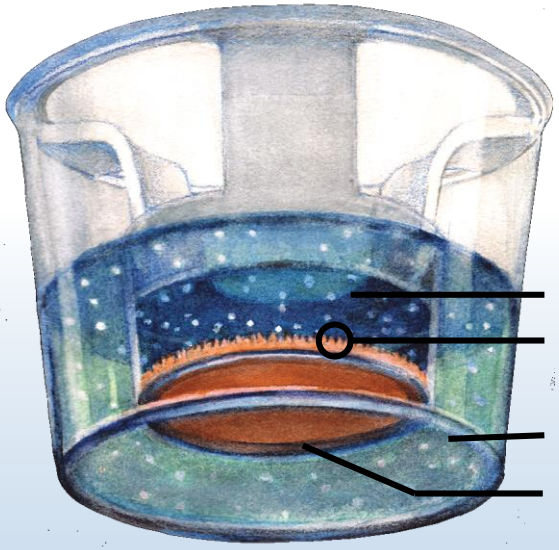
BDDCS as alternative to BCS?

- Shares the same liability depending on mass-balance data.
- ≥ 85% of dose recovered as oxidative/conjugated metabolites → > 15% excreted unchanged in urine disqualifies – results in many false negative (felbamate, paliperidone, pregabaline, valproic acid, ….)
- The purpose of BCS is to facilitate biowaivers of in vivo bioequivalence studies for drugs that exhibit no significant intestinal absorption problems.
- **In contrast, the purpose of BDDCS is to predict the drug disposition of NMEs as well as potential drug– drug interactions for NMEs and drugs on the market with respect to the intestine and liver. Rather, BDDCS helps prioritize what interactions should and should not be investigated**

Moving towards *in vitro* - back to the initial idea of BCS

- **If 2 drug products containing the same drug have the same conc/time profile at the intestinal membrane surface they will have the same rate and extent of absorption** (*Amidon et al., 1995*)
- Fundamental starting point, Fick's law: Jw= Pw x Cw with Jw = drug flux (mass/area/time) through intestinal wall; Pw = permeability of the membrane and Cw = drug conc at intestinal surface.
  - ➢Pw or Peff is intended to be not affected by any change in formulation (constant) needs to be tested once for the compound – in vitro test!
  - ➢Cw is determined by the solubility of an API and eventually by the dissolution rate of the formulation –needs to be tested for the formulation.

A Validated System (e.g. Caco-2 - Transwell system) ?

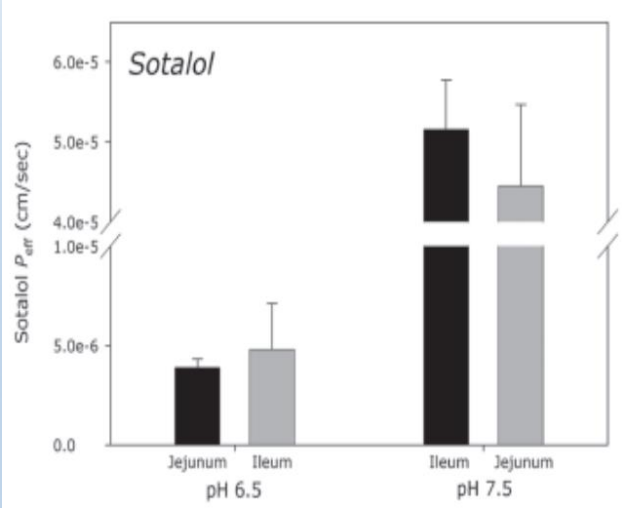


$$P_{app} = \frac{dC_r/dt \times V_r}{A \times C_o}$$

$$ER = \frac{P_{app\ (B \rightarrow A)}}{P_{app\ (A \rightarrow B)}}$$

Permeability and transporter function

- Days in culture: 21-28
- Passage number: 58-76
- Donor pH: 6.5 and 7.4



Adapted froim Bhoopathy, 2014

Standardisation via Permeability Probe Compounds (Annex 1, M09 draft)

Table 2. Examples of model drugs for permeability assay method validation

Group	Drug
High Permeability (f_a ≥85 percent)	Antipyrine
	Caffeine
	Ketoprofen
	Naproxen
	Theophylline
	Metoprolol
	Propranolol
	Carbamazepine
	Phenytoin
	Disopyramide
	Minoxidil
Moderate Permeability (f_a = 50-84 percent)	Chlorpheniramine
	Creatinine
	Terbutaline
	Hydrochlorothiazide
	Enalapril
	Furosemide
	Metformin
	Amiloride
	Atenolol
	Ranitidine
Low Permeability (f_a < 50 percent)	Famotidine
	Nadolol
	Sulpiride
	Lisinopril
	Acyclovir
	Foscarnet
	Mannitol

Permeability Values for each model drug
Plot of Extent of Absorption as a function of Permeability with
High permeabilty class boundary and
Selected high permeability internal standard

FDA evaluation of *in vitro* vs. *in vivo* permeability assessment

- 18 drugs had *in vitro* (Caco-2) and in vivo, either mass balance or abs BA data.
- In case of substantial amounts (> 15%) of metabolites in feces (N = 7 drugs) those were assumed to be formed via oxidative / conjugative pathway.
- Under this assumption all 18 drugs show that Caco-2 results are similar to those seen via mass balance / absolute BA studies.
- Nine (9) drugs with only Caco-2 data showing high permeability; based on *in-vivo* information on these in the public domain it trended in the right direction
- Results seen so far have shown positive correlation between in Caco-2 and in-vivo; few examples of false-negatives with Caco-2 but no case of false-positive

Mehul Mehta, FDA (04/25/2017)

Summary and Conclusion

- Permeability is the fundamental definition and deduction from bioavailability or fraction absorbed is the indirect proof.
- Mass Balance as in vivo approach has some methodological limitations potentially leading to false negative
  – *Some false negative from mass balance may be eligible as BCS I due to in vitro methodology*
- The in vitro permeability assessment via Caco-2 cell assays is closer to the fundamental definition
- Validation and Standardisation is a MUST
- So far, no clear case of false positive high permeability with Caco-2

ICH M09 Draft in 2018 “Harmonized Permeability”

- Human PK, Absorption ≥ 85 %
  - In vitro permeability (validated & standardised Caco-2 assay, no active transport)
  - Literature data (details of experimental data required)

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ICH harmonisation for better health

INTERNATIONAL CONCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED BIOWAIVERS

M9

Draft version

Endorsed on 7 June 2018

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

European Medicines Agency

London, 20 January 2010
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Some feedback on the draft

- Why not include other permeability measurement approaches (in vitro, in situ), if appropriately validated (as in FDA guideline)?
- Limiting to Caco-2 may discourage scientific progress? license needed for Caco-2
- why restriction to passively transported if only in vitro data? Pregabaline, Levodopa, Pramipexole are BCS I and highly permeable but substrate of active uptake transport ; verapamil substrate of efflux but BCS I
- How much do we expect excipients in general or quantitative deviation of an excipient to modify transporter action if dissolution rate and hence luminal conc. of a drug is the same (dissolution faster than gastric emptying)? potentially some surfactants can increase permeability – **no clear-cut evidence in human** (however preclinical and in vitro evidence makes these of concern)

Back-up

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High permeability proven via *in vivo* PK

- absolute bioavailability is ≥ 85%
- ≥ 85% of the administered dose is recovered in urine as unchanged (parent drug)
- sum of parent drug, Phase 1 oxidative and Phase 2 conjugative metabolites ≥ 85% in urine
- sum of urinary total drug material (parent and metabolites) **and** fecal recovery of drug derived metabolites is ≥ 85%.
  - Regarding metabolites in feces only oxidative and conjugative metabolites can be considered.
  - Parent in feces: biliary excretion, intestinal secretion or originates from an unstable metabolite, e.g., glucuronide, sulphate, N-oxide that has been converted back to the parent by the action of microbial organisms

- Human *in vivo* data derived from published literature may be acceptable (necessary details of the testing /underlying data! to make a judgement regarding the quality of the results)

Harmonization on *in vitro* test as alternative proof of high permeability

- "Permeability can be also assessed by **validated and standardized*** *in vitro* methods using **Caco-2 cells**(see Annex I). The results from Caco-2 permeability assays should be discussed in the context of available data on human pharmacokinetics. *In vitro* cell permeability assays (Caco-2) used in support of high permeability should be appropriately validated and standardized as outlined in Annex 1. If high permeability is inferred by means of an *in vitro* cell system, permeability **independent of active transport** should be proven as outlined in Annex I, "Assay Considerations"
  Additional pre-requisites: Proof of stability in GI tract (also for mass balance data); incubation in compendial and simulated gastric and intestinal fluids

* rank-order using zero, low (<50%), moderate (50 – 84%), and high (≥85%) permeability model drugs; The test drug is considered highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.