BCS From Theory to Applications in Product Development and Drug Product Regulation

Gordon L. Amidon
College of Pharmacy
University of Michigan
Ann Arbor, MI 48109-1065
Email: glamidon@umich.edu

Amman, Jordan: September 23-24, 2013

What is the Role of the Pharmaceutical Scientist?

Deliver High Pharmaceutical Quality Product to the patient

What is high Pharmaceutical Quality?

- The product performs according to the **label claims.**
- How good are label claims?
- Pharmaceutical Standards!
- How do we set them?

Why is BE Important?

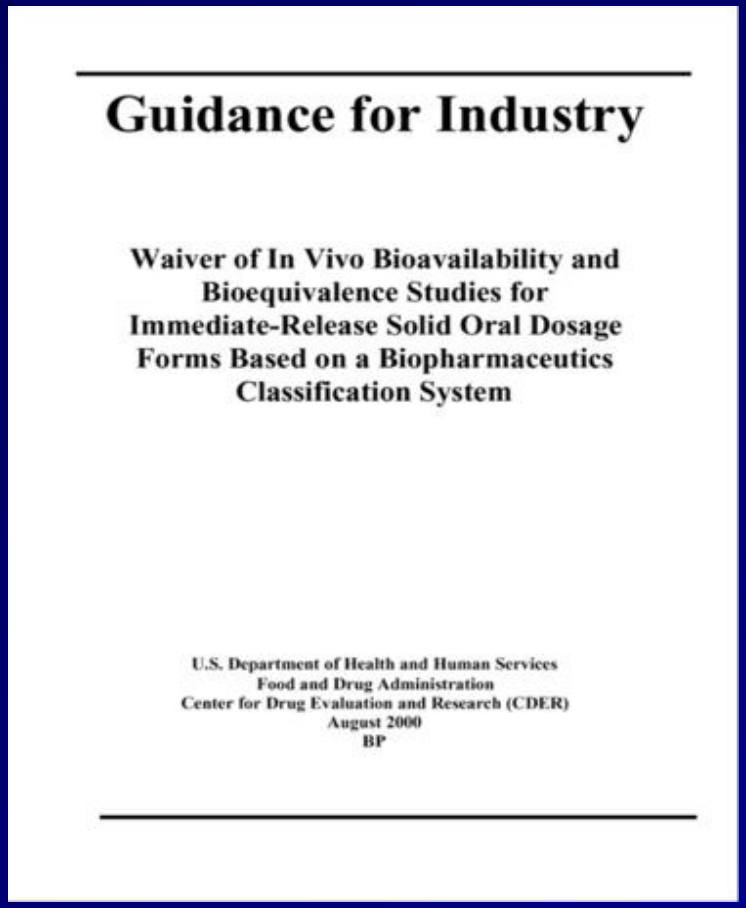
BE connects the product in the bottle with the claims on the label!

Label

"BE"

Product

FDA BCS Guidance



Guidance for Industry

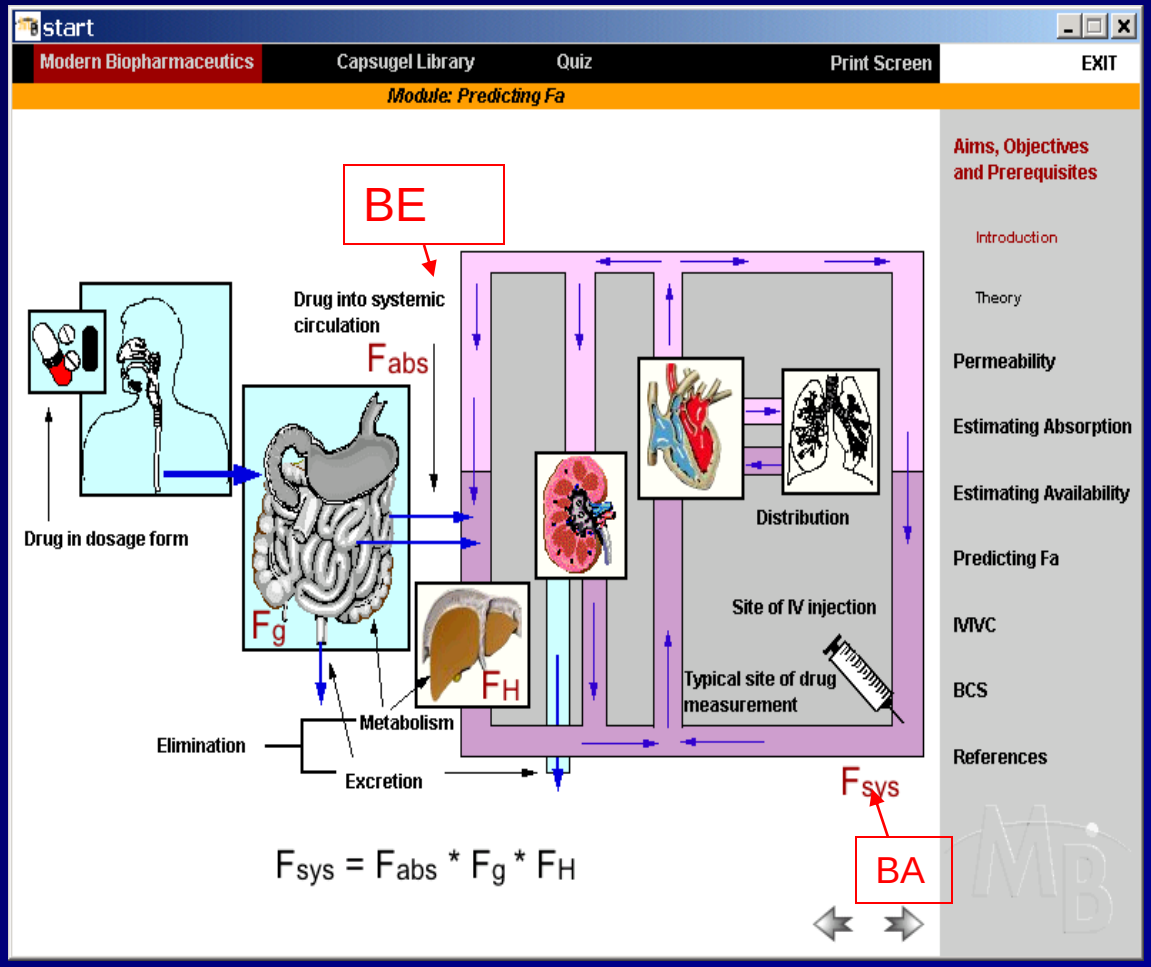
Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

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

Biopharmaceutics Class	*Solubility*	*Permeability*
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

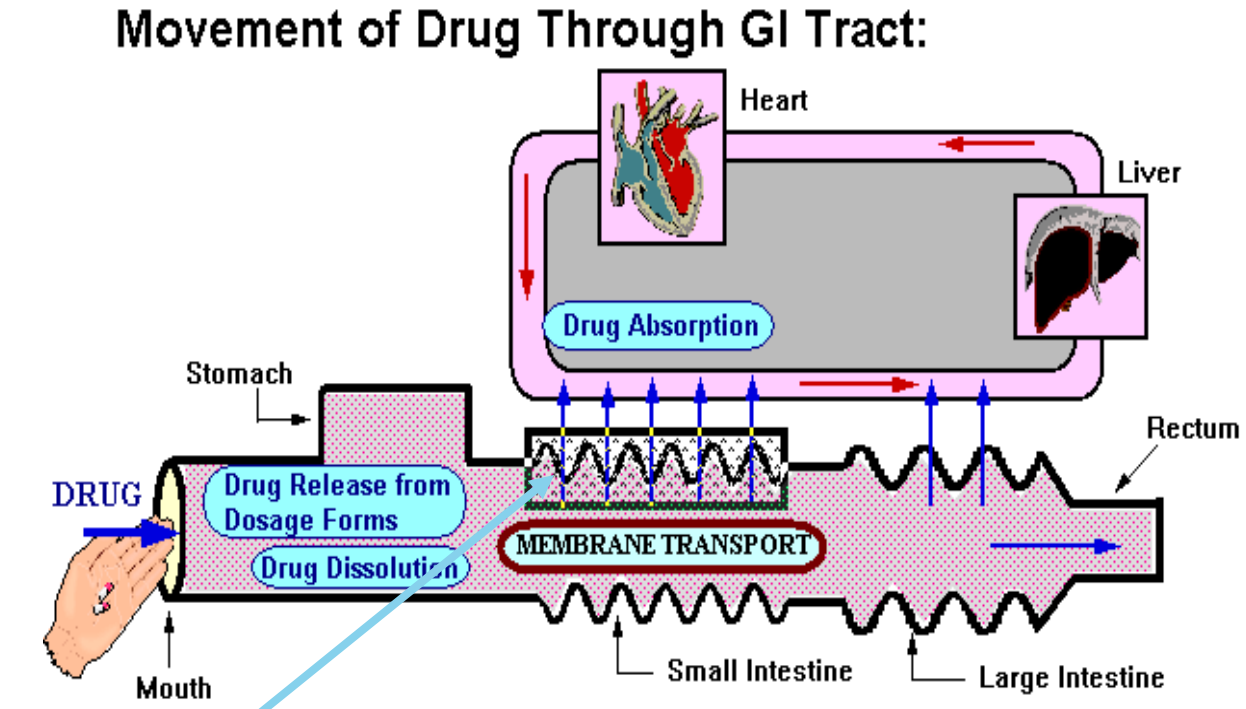
- BCS Class I Biowaivers
- BCS Class III Biowaivers Recommended and Under Consideration

Systemic (BA) vs. Oral Transport View (BE)



- The Science of BE is at the Absorption Site

BCS takes a mechanistic approach to setting bioequivalence standards: Mass Transport in the GI Tract



$$\text{Flux} = j = P_{eff} \cdot C$$

First Principle of Bioequivalence

If a drug from two products are presented to the Intestinal Surface *Equivently* they will be Bioequivalent

Diffusion vs. Pharmacokinetic Views of Absorption

Diffusion

$$J = (dM / dt)1 / A$$

$$= P \cdot \Delta C \cong P \cdot C$$

$$P = cm / \sec.$$

Pharmacokinetic

$$dC / dt = (dM / dt)1 / V$$

$$= k_a \cdot \Delta C \cong k_a \cdot C$$

$$k_a = 1 / \sec$$

$$k_a = (S / V) \cdot P_{eff}$$

Software e.g. GastroPlus®

Absorption Rate Coefficient: k_a ~Local Permeability(Peff)

Transport

$$J = (1/A)(dM/dt) = P_{eff} \cdot C$$

PK

$$dC/dt = (1/V)dM/dt = k_a C$$

Permeability ~ Absorption Rate Coefficient(constant)

Equating dM/dt : $A \cdot P_{eff} \cdot C = V \cdot k_a C$

$$k_a = (A/V)P_{eff}$$

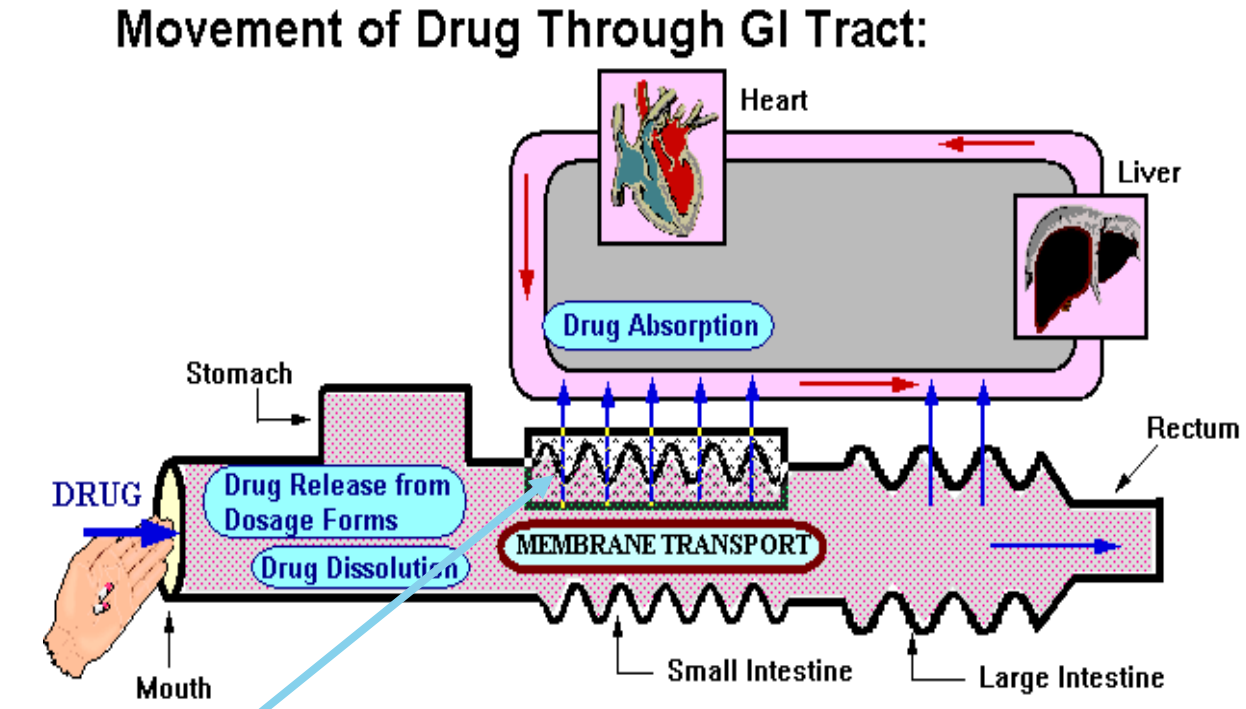
$$k_a = (2/R)P_{eff} \cong P_{eff}$$

$$R \approx 2cm(1.75)$$

$$k_a \sim P_{eff}$$

Numerically (Units differ: 1/sec vs. cm/sec)

BCS takes a mechanistic approach to setting bioequivalence standards: Mass Transport in the GI Tract



$$\text{Flux} = j = P_{eff} \cdot C$$

Biopharmaceutics Classification System (BCS): Basis

$$M(t) = \int_0^t \iint_A (P_{eff} \cdot C)\, dA\, dt$$

Absorption per unit area per unit time

Why is BE Important?

BE connects the product in the bottle with the claims on the label!

Label

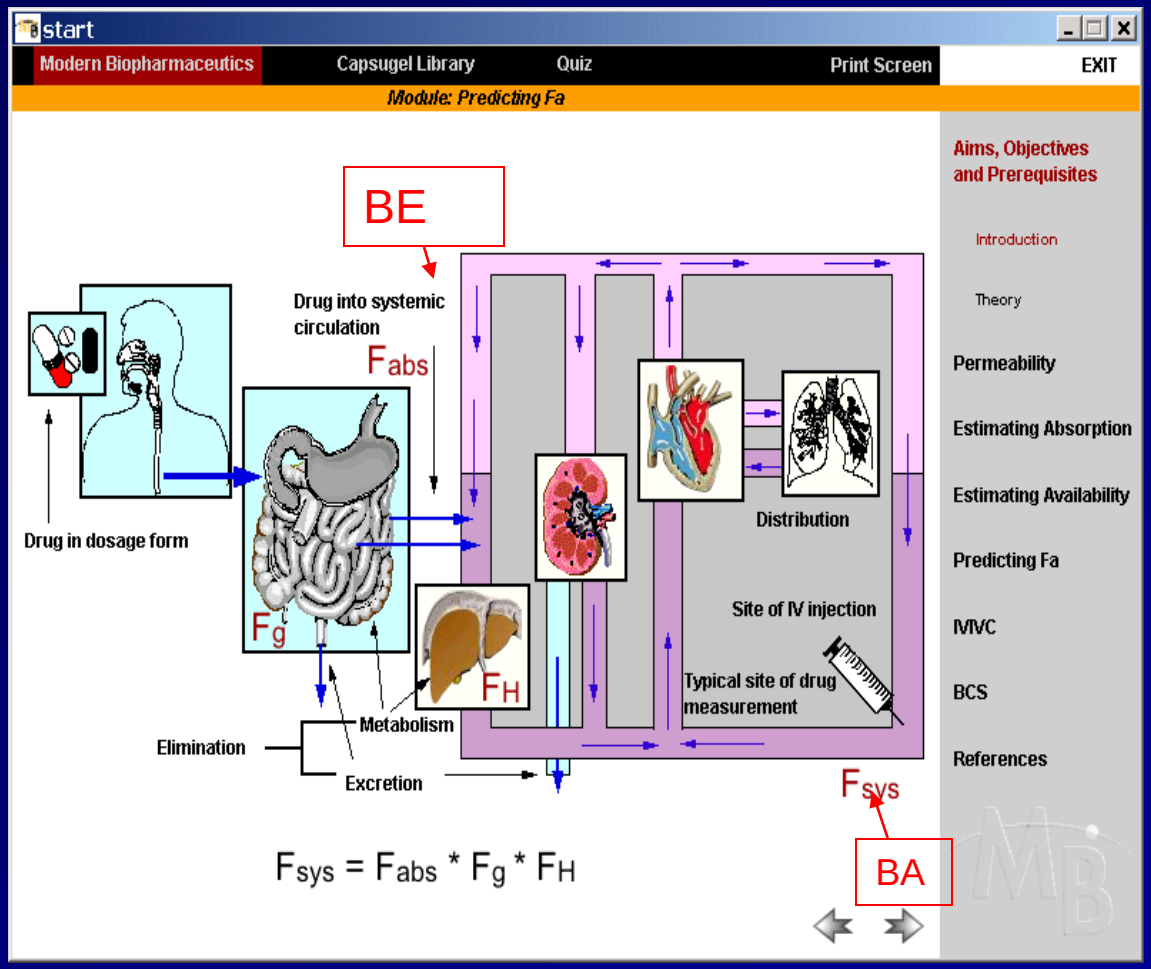
"BE"

Product

Bioequivalence (BE) Today

- Historically a Relative Bioavailability (BA) Based View
  - Misses the underlying scientific issues
    - *IN Vivo* Dissolution
- BE Testing is Same Drug
  - Once Absorbed PK is the Same
- The Science of BE is at the Absorption Site
  - For Oral Dosage Form in the GI Tract
- The Question is: What is the **Best** BE Test

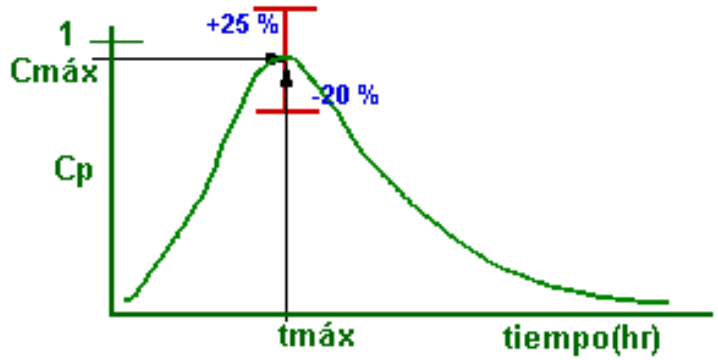
Systemic (BA) vs. Gut View (BE)



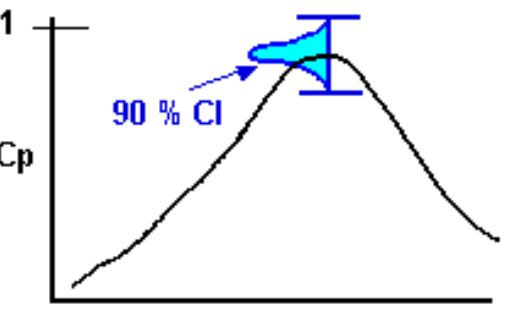
- The Science of BE is at the Absorption Site

Ejemplo de test de Bioequivalencia a partir del Cmáx:

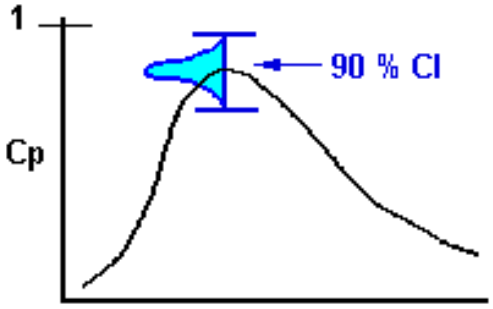
Perfil de concentración del fármaco de referencia



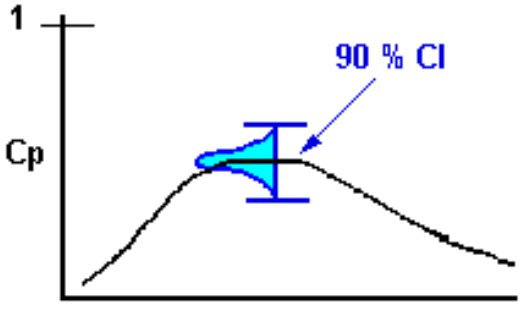
Perfiles de concentración del fármaco problema:



¿Bioequivalente?



¿Bioequivalente?



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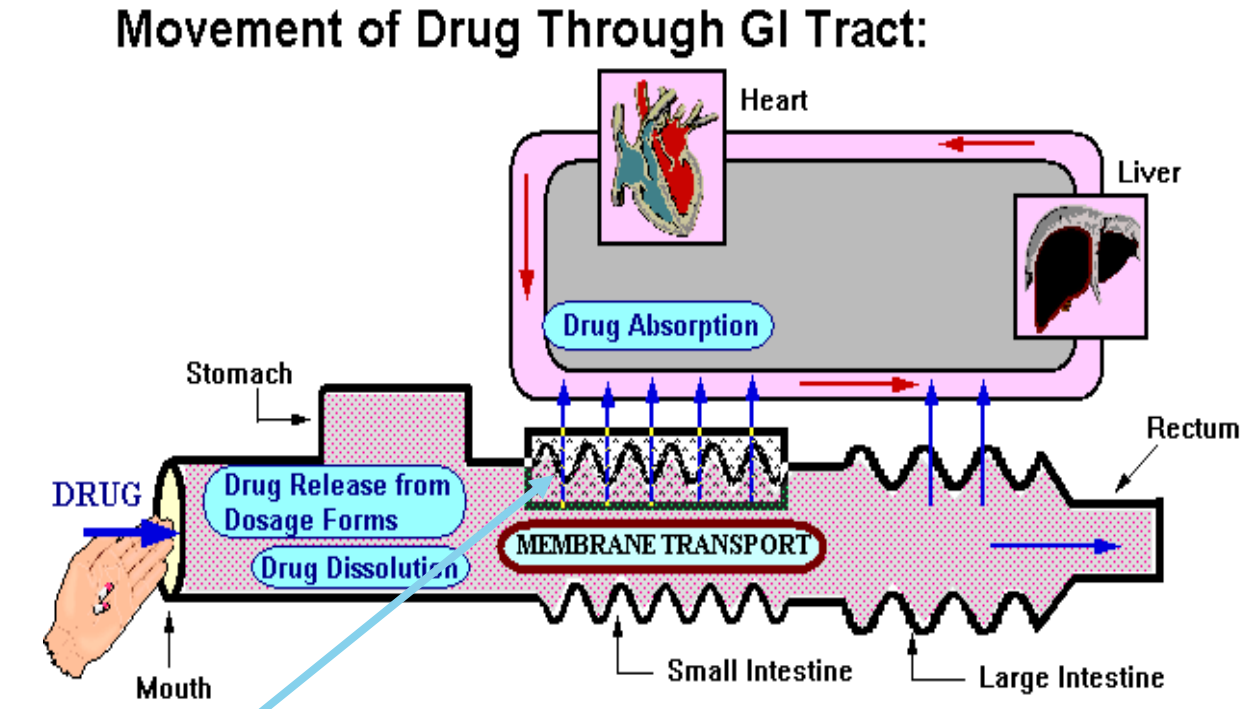

$$\text{Flux} = j = P_{eff} \cdot C$$

August 2000 FDA Guidance

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U.S. Department of Health and Human Services
Food and Drug Administration
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August 2000
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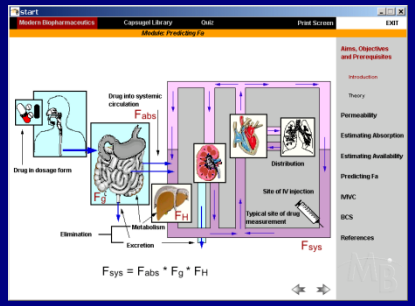
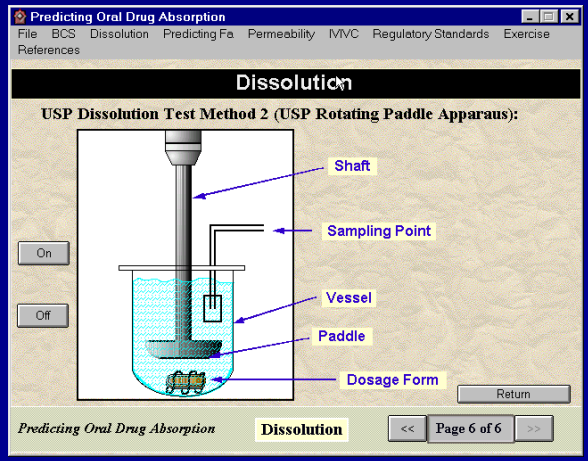
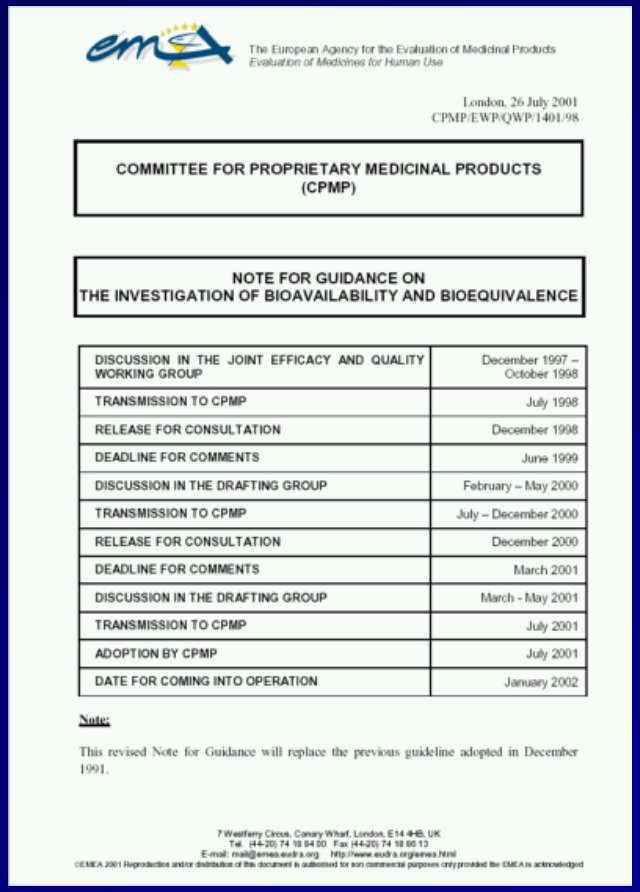
A Theoretical Basis for a Biopharmaceutic Drug Classification: The Correlation of *in Vitro* Drug Product Dissolution and *in Vivo* Bioavailability



G.L. Amidon et. al., Pharmaceutical Research, 12, 413 (1995).



EMEA/CPMP and FDA/BCS



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 26 July 2001
CPMP/EWP/QWP/1401/98

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING GROUP	December 1997 – October 1998
TRANSMISSION TO CPMP	July 1998
RELEASE FOR CONSULTATION	December 1998
DEADLINE FOR COMMENTS	June 1999
DISCUSSION IN THE DRAFTING GROUP	February – May 2000
TRANSMISSION TO CPMP	July – December 2000
RELEASE FOR CONSULTATION	December 2000
DEADLINE FOR COMMENTS	March 2001
DISCUSSION IN THE DRAFTING GROUP	March - May 2001
TRANSMISSION TO CPMP	July 2001
ADOPTION BY CPMP	July 2001
DATE FOR COMING INTO OPERATION	January 2002

Note:

This revised Note for Guidance will replace the previous guideline adopted in December 1991.

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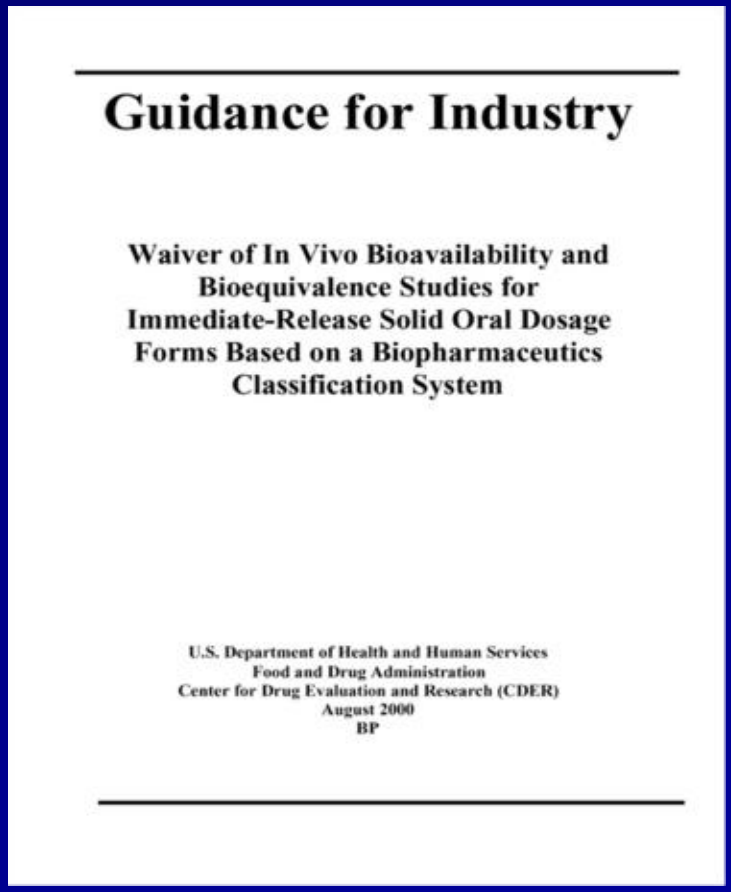

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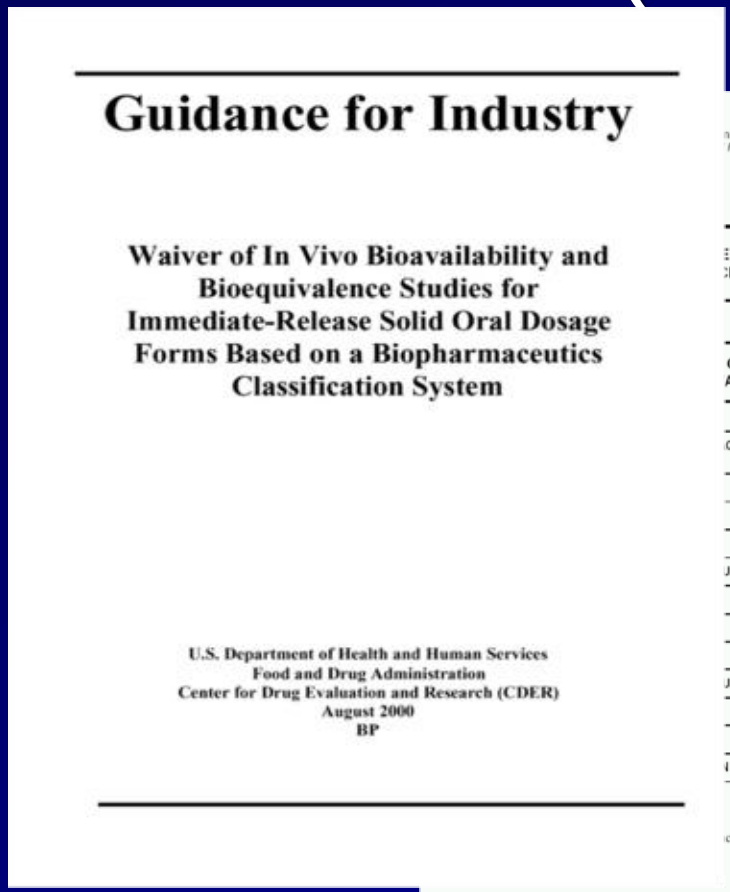
FDA/BCS, EMA/CPMP, WHO BE Recommendations (2000-2010)



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August 2000
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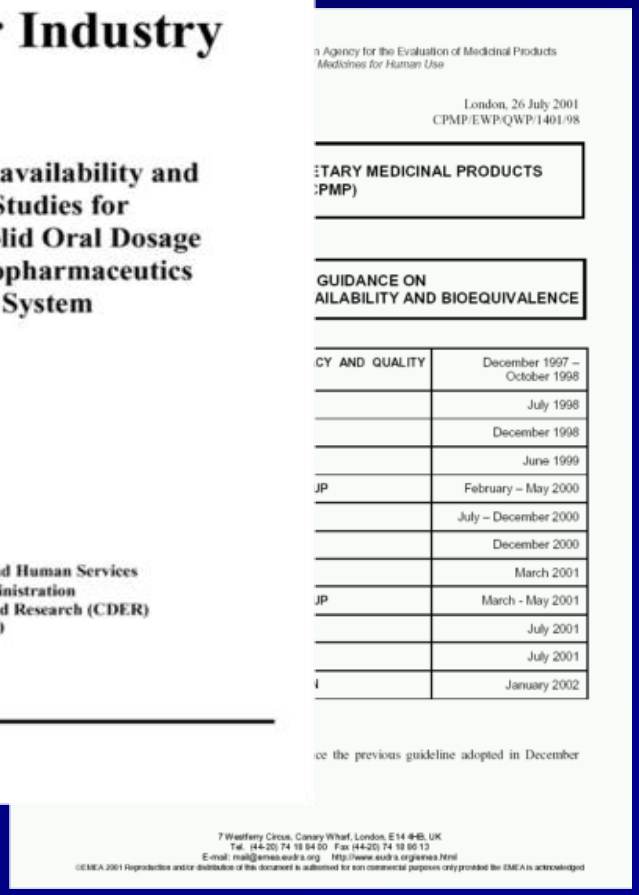

Agency for the Evaluation of Medicinal Products
Medicines for Human Use

London, 26 July 2001
CPMP/EWP/QWP/1401/98

ETARY MEDICINAL PRODUCTS
CPMP)

GUIDANCE ON
AILABILITY AND BIOEQUIVALENCE

CY AND QUALITY	December 1997 – October 1998
	July 1998
	December 1998
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JP	February – May 2000
	July – December 2000
	December 2000
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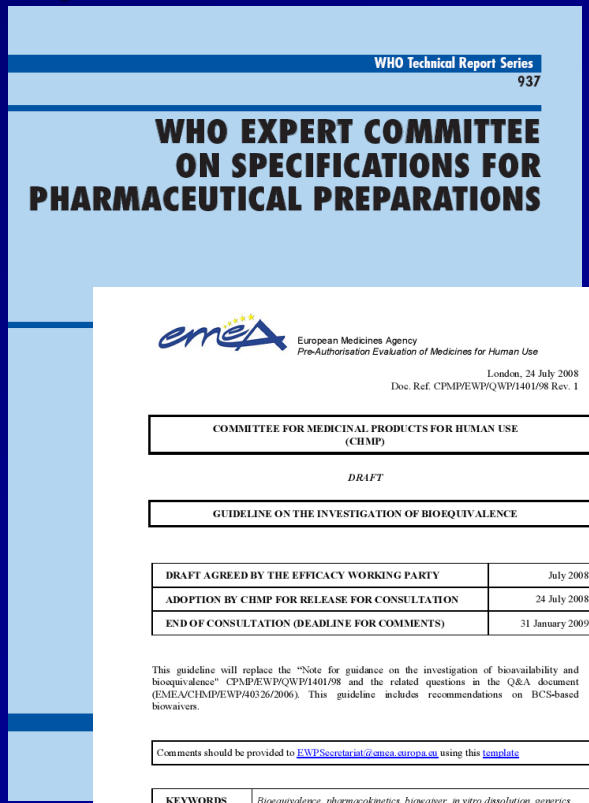

WHO Technical Report Series
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WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 24 July 2008
Doc. Ref. CPMP/EWP/QWP/1401/98 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

DRAFT AGREED BY THE EFFICACY WORKING PARTY	July 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 July 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 January 2009

This guideline will replace the "Note for guidance on the investigation of bioavailability and bioequivalence" CPMP/EWP/QWP/1401/98 and the related questions in the Q&A document (EMEA/CHMP/EWP/40326/2006). This guideline includes recommendations on BCS-based biowaivers.

Comments should be provided to EWPSecretariat@emea.europa.eu using this template

KEYWORDS	*Bioequivalence, pharmacokinetics, biowaiver, in vitro dissolution, generics*

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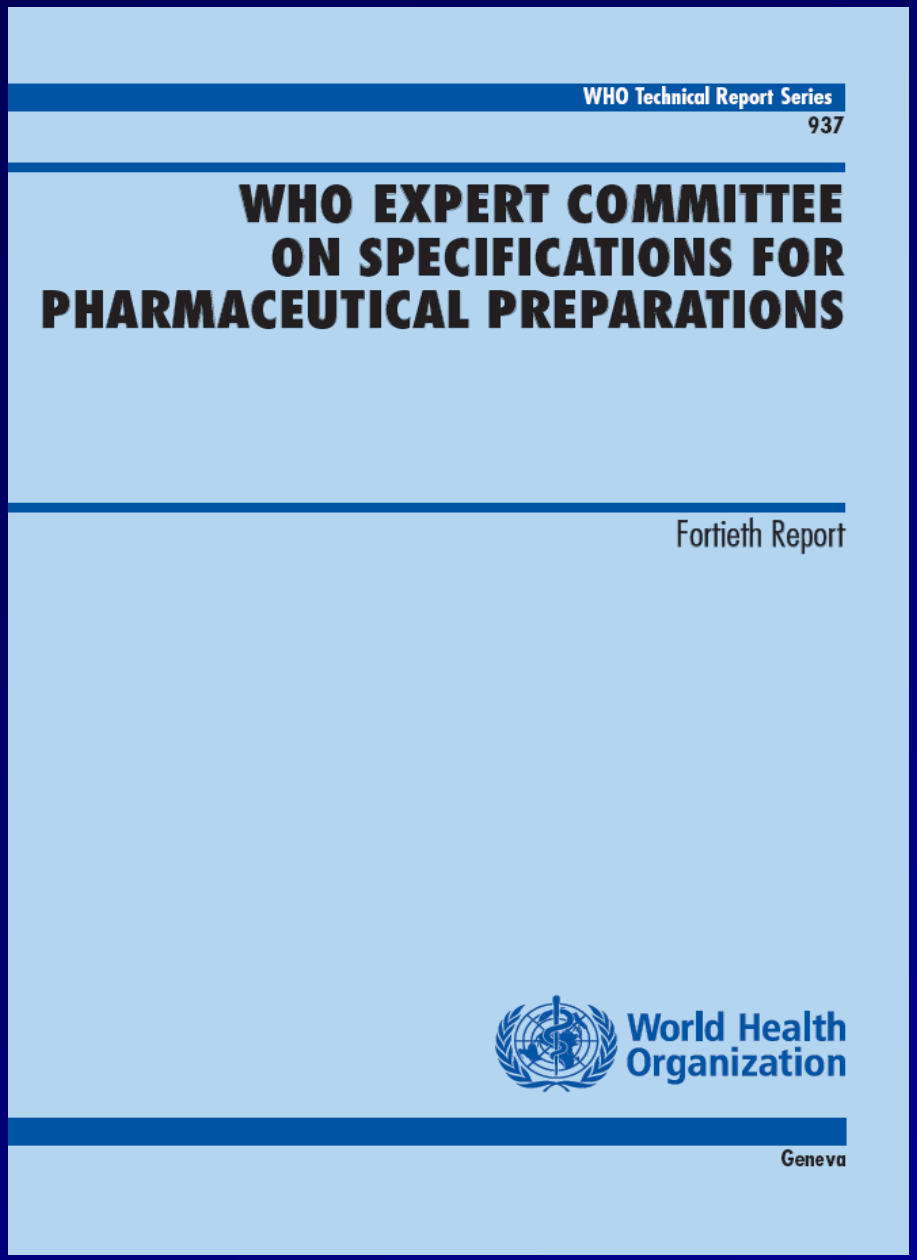

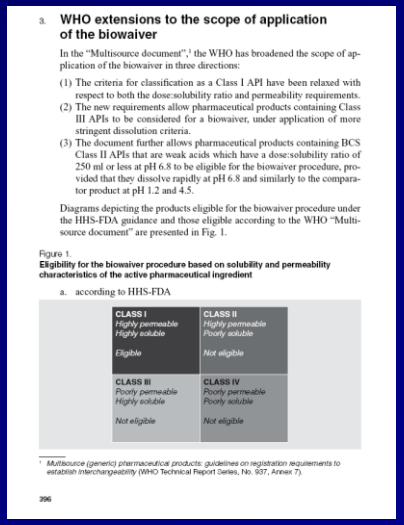

3. **WHO extensions to the scope of application of the biowaiver**

In the "Multisource document",[1] the WHO has broadened the scope of application of the biowaiver in three directions:

(1) The criteria for classification as a Class I API have been relaxed with respect to both the dose:solubility ratio and permeability requirements.
(2) The new requirements allow pharmaceutical products containing Class III APIs to be considered for a biowaiver, under application of more stringent dissolution criteria.
(3) The document further allows pharmaceutical products containing BCS Class II APIs that are weak acids which have a dose:solubility ratio of 250 ml or less at pH 6.8 to be eligible for the biowaiver procedure, provided that they dissolve rapidly at pH 6.8 and similarly to the comparator product at pH 1.2 and 4.5.

Diagrams depicting the products eligible for the biowaiver procedure under the HHS-FDA guidance and those eligible according to the WHO "Multisource document" are presented in Fig. 1.

Figure 1.
Eligibility for the biowaiver procedure based on solubility and permeability characteristics of the active pharmaceutical ingredient

a. according to HHS-FDA

CLASS I *Highly permeable* *Highly soluble* *Eligible*	CLASS II *Highly permeable* *Poorly soluble* *Not eligible*
CLASS III *Poorly permeable* *Highly soluble* *Not eligible*	CLASS IV *Poorly permeable* *Poorly soluble* *Not eligible*

[1] *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO Technical Report Series, No. 937, Annex 7).

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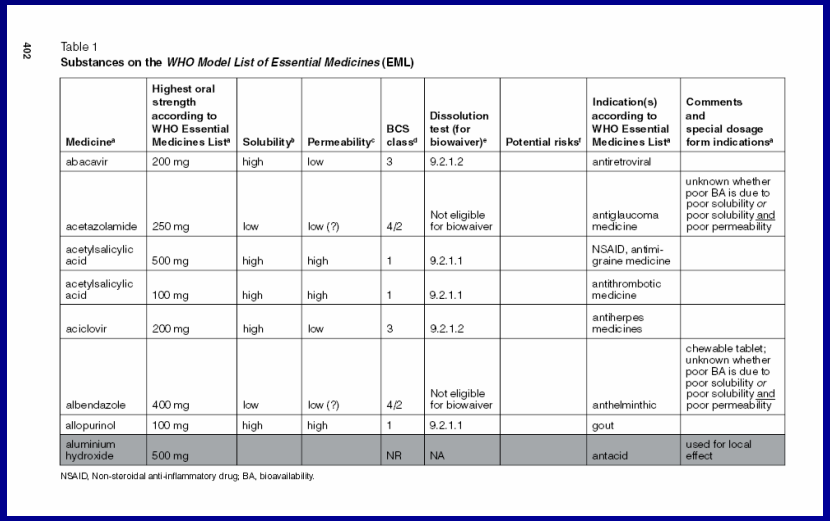

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Table 1
Substances on the *WHO Model List of Essential Medicines* (EML)

Medicine[a]	Highest oral strength according to WHO Essential Medicines List[a]	Solubility[b]	Permeability[c]	BCS class[d]	Dissolution test (for biowaiver)[e]	Potential risks[f]	Indication(s) according to WHO Essential Medicines List[a]	Comments and special dosage form indications[a]
abacavir	200 mg	high	low	3	9.2.1.2		antiretroviral	
acetazolamide	250 mg	low	low (?)	4/2	Not eligible for biowaiver		antiglaucoma medicine	unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
acetylsalicylic acid	500 mg	high	high	1	9.2.1.1		NSAID, antimigraine medicine	
acetylsalicylic acid	100 mg	high	high	1	9.2.1.1		antithrombotic medicine	
aciclovir	200 mg	high	low	3	9.2.1.2		antiherpes medicines	
albendazole	400 mg	low	low (?)	4/2	Not eligible for biowaiver		anthelminthic	chewable tablet; unknown whether poor BA is due to poor solubility *or* poor solubility and poor permeability
allopurinol	100 mg	high	high	1	9.2.1.1		gout	
aluminium hydroxide	500 mg			NR	NA		antacid	used for local effect

NSAID, Non-steroidal anti-inflammatory drug; BA, bioavailability.

- Annex 7 page 347
- Annex 8 page 391

Pan American Health Organization

Regional Office of the World Health Organization

PAN AMERICAN NETWORK FOR DRUG REGULATORY HARMONIZATION

FRAMEWORK FOR IMPLEMENTATION OF EQUIVALENCE REQUIREMENTS FOR PHARMACEUTICAL PRODUCTS

Document for Public Opinion

WORKING GROUP ON BE

WHO (BE) Recommendations

- Solubility and Permeability
  - Same as (~)FDA and EMEA
    - Dissolution and solubility pH=6.8 (rather than 7.5)
- Dissolution: Very Rapid, Rapid, Not Rapid
- Recommends Classes for drugs on (WHO) EML
- Recommends dissolution ‘Biowaivers’ for Class I, III, and some Class II Drugs (IIa)
- Extends BCS Biowaivers to 60% of Drug Products

What is the BCS? Permeability and Solubility Classification

The BCS is a scientific framework for classifying drugs based on their aqueous solubility and intestinal permeability and setting the best Bioequivalence Test.

Biopharmaceutics Class	***Solubility***	***Permeability***
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

Biopharmaceutics Classification System (BCS): Basis

$$M(t) = \int_0^t \iint_A (P_{eff} \cdot C)\, dA\, dt$$

Absorption per unit area per unit time

Maximum Flux (Absorption)

$$dM / dt(1/A) = J_{\max} = P_{eff} \cdot C_s$$

= Mass Absorbed per Unit Time per Unit Area

C_s = Solubility

High Solubility Drug

FDA Glass of Water= 8 oz.
(240 ml)

- Vs = Volume of Solution <250 ml,
- pH=1-7.5
- Highest Dose Strength
- $Do=Dose/250/C_s$ <1

Diffusion vs. Pharmacokinetic Views of Absorption

Diffusion

$$J = (dM / dt)1 / A$$
$$= P \cdot \Delta C \cong P \cdot C$$
$$P = cm / \sec.$$

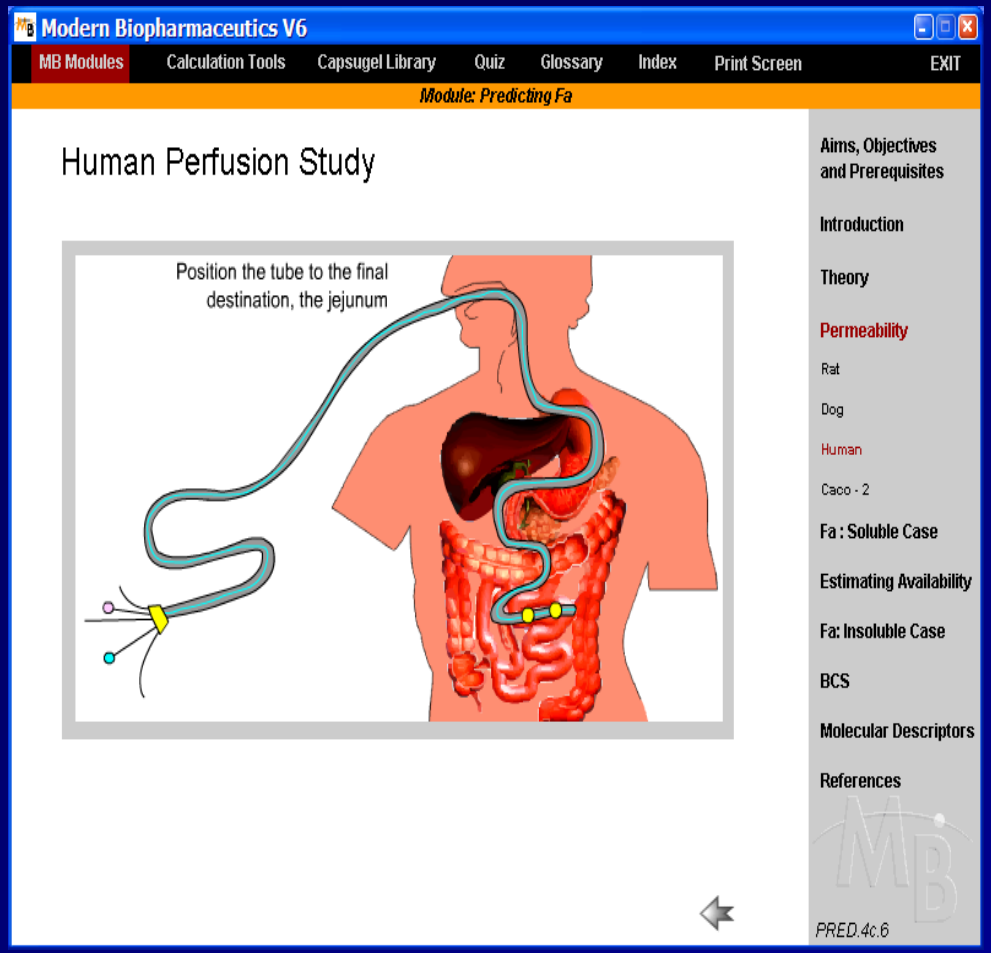
Pharmacokinetic

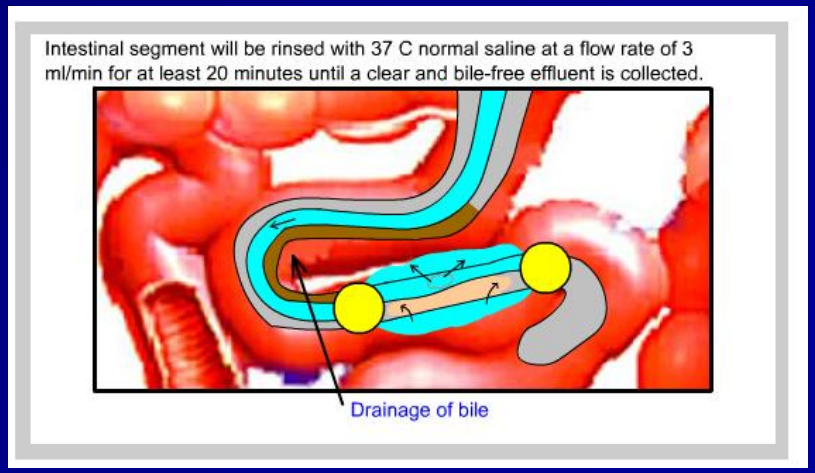
$$dC / dt = (dM / dt)1 / V$$
$$= k_a \cdot \Delta C \cong k_a \cdot C$$
$$k_a = 1 / \sec$$

$$k_a = (S / V) \cdot P_{eff}$$

Software e.g. GastroPlus®

Human Permeability





N. Takamatsu, et al. Pharm.Res., 14, 1127 (1997).

Human Jejunal Permeability (The ‘Gold’ Standard)

Xenobiotica, October November 2007; 37(10 11): 1015 1051

Intestinal permeability and its relevance for absorption and elimination

H. LENNERNÄS

Biopharmaceutics, Uppsala University, Uppsala, Sweden

(*Received 21 September 2006; accepted 25 September 2007*)

Abstract

Human jejunal permeability (P_{eff}) is determined in the intestinal region with the highest expression of carrier proteins and largest surface area. Intestinal P_{eff} are often based on multiple parallel transport processes. Site-specific jejunal P_{eff} cannot reflect the permeability along the intestinal tract, but they are useful for approximating the fraction oral dose absorbed. It seems like drugs with a jejunal $P_{eff} > 1.5 \times 10^{-4}$ cms^{-1} will be completely absorbed no matter which transport mechanism(s) are utilized. Many drugs that are significantly effluxed *in vivo* have a rapid and complete intestinal absorption (i.e. >85%) mediated by passive transcellular diffusion. The determined jejunal P_{eff} for drugs transported mainly by absorptive carriers (such as peptide and amino acid transporters) will accurately predict the fraction of the dose absorbed as a consequence of the regional expression. The data also show that: (1) the human intestinal epithelium has a large resistance towards large and hydrophilic compounds; and (2) the paracellular route has a low contribution for compounds larger than approximately molecular weight 200. There is a need for more exploratory *in vivo* studies to clarify drug absorption and first-pass extraction along the intestine. One is encouraged to develop *in vivo* perfusion techniques for more distal parts of the gastrointestinal tract in humans. This would stimulate the development of more relevant and complex *in vivo* absorption models and form the basis for an accurate physiologically based pharmacokinetic modelling of oral drug absorption.

Keywords: *Intestinal permeability, intestinal secretion, intestinal efflux, drug absorption, bioavailability, biopharmaceutics classification system, intestinal transporters, pharmacology, pharmacokinetics, intestinal perfusion, P-glycoprotein*

Introduction

The gastrointestinal tract has several important functions besides the absorption and secretion of drugs. It must also absorb nutrients rapidly and at the same time act as an efficient barrier against potentially hazardous bacteria and toxins. Further, gut-associated

Correspondence: H. Lennernäs, Biopharmaceutics, Uppsala University, Uppsala, Sweden. E mail: hans.lennernas@farmaci.uu.se

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Table I. Biopharmaceutics classification system (BCS) classification of 28 drugs based on human effective permeability (P_{eff}) and dose number. Each P_{eff} value was determined *in vivo* in the proximal jejunum in humans with a single-pass approach at pH 6.5 (phosphate buffer) and under isotonic conditions. Twenty-four of the drugs were evaluated at Uppsala University, Sweden, and five were evaluated at the University of Michigan, USA.

Drug	Human *in vivo* permeability ($\times 10^{-4}$ cms^{-1})	Dose number*	BCS Class	f_a (%)	Laboratory
α-Methyldopa	0.10	0.1	III	55 65	UU
Amiloride	1.6	0.4 0.8	I	80 90	UU
Amoxicillin#	0.30	0.9	III	45 75	UU
Antipyrine	5.60	0.20	I	100	UU
Atenolol	0.20	0.02	III	50 60	UU
Carbamazepine	4.30	80	II	>90	UU
Cephalexin	1.56	2	II	>90	UM
Cimetidine	0.26	3	III	75	UU
Cyclosporine	1.61	350	II	>90	UM
Desipramine HCl	4.50	<0.03	I	100	UU
Enalapril maleate	1.57	0.003	(I)**	65	UM
Enalaprilat	0.20	0.003	III	8	UU
Fexofenadine	0.07	0.32	III	5 10	UU
Fluvastatin sodium	2.40	<0.9	I	95	UU
Furosemide	0.05	30	IV	40 60	UU
Hydrochlorothiazide	0.04	0.2	III	55	UU
Isotretinoin	0.99	>20	II	90	UU
Inogatran	0.03	<0.001	III	5 10	UU
Ketoprofen	5.70	0.2	I	100	UU
L-dopa	3.40	1.0	(I)***	100	UU
Lisinopril	0.33	0.002	III	35	UU
Losartan	1.15	0.004	III	100	UU
Metoprolol	1.34	0.0004	I	95	UU
Naproxen	8.50	0.06	I	100	UU
Piroxicam	6.65	2.5	II	100	UM
Propanolol	2.81	0.01	I	100	UU
Ranitidine	0.27	0.01	III	50 60	UM
Terbutaline	0.30	0.01	III	40 50	UU
Valacyclovir	1.66	0.02	I***	>80	UM
R-verapamil	6.80	0.004	I	100	UU
S-verapamil	6.80	0.004	I	100	UU

*Human P_{eff} was determined at a concentration based on the most common clinical dose dissolved in 250 ml. For low solubility concentration, the highest possible drug concentrations were applied.
**Dose number $dose/V_0/C_{s\ min}$ (highest dose strength/initial gastric volume (250 ml)) min^{-1}/min solubility.
***High permeability due to carrier-mediated absorption, currently not included in BCS Class I.
UU, Uppsala University, Sweden; UM, University of Michigan, USA.
#75% at 500 mg 45% at 3000 mg.
Data are from: Lennernas et al. (1992; 1993; 1994, 1997a, 2002b); Fagerholm et al. (1995; 1996, 1997, 1999); Lindahl et al. (1996); Lennernas (1997, 1998); Sodergholm et al. (1997); Takamatsu et al. (1997, 2001); Sandström et al. (1998b, 1999b); Winiwarter et al. (1998, 2003); Sun et al. (2002); Chiu et al. (2003); Petri et al. (2003, 2006b); and Tannergren et al. (2003a, b; 2004).

gastrointestinal passage of a solid meal with gamma-scintigraphy. Read et al. reported that the gastric emptying half-life changed from 1.2 ± 0.32 to 1.5 ± 0.35 h, and the small intestinal transit time decreased from 3.6 ± 1.33 to 2.0 ± 0.99 h (mean ± standard deviation (SD)). Thus, the effects of the tube on gastric emptying are minimal and do not question the pharmaceutical relevance of drug absorption data collected using these perfusion methods. Further support for this conclusion is reported by Näslund et al. (2000) who clearly showed that there was no difference in gastric emptying between the following

F_{abs} vs.P_{eff} (cm/sec)
(Human Jejunum)

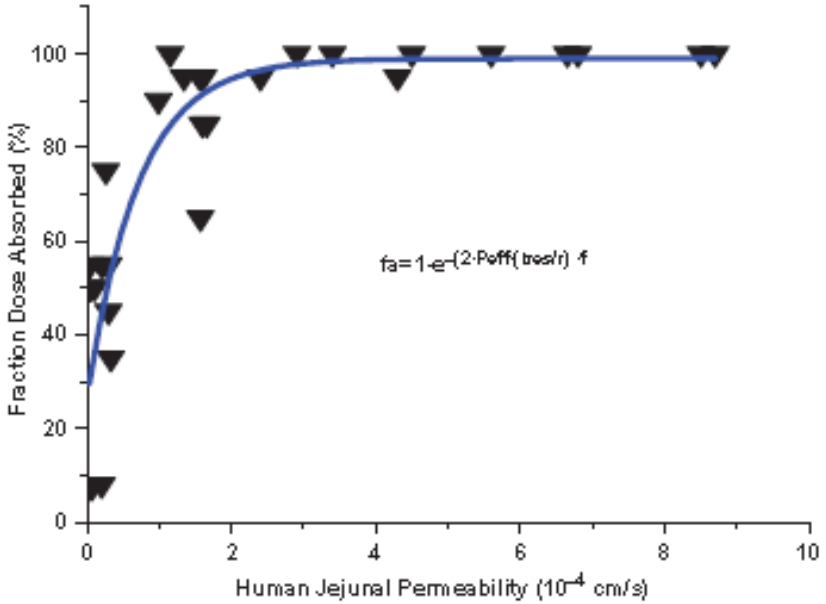
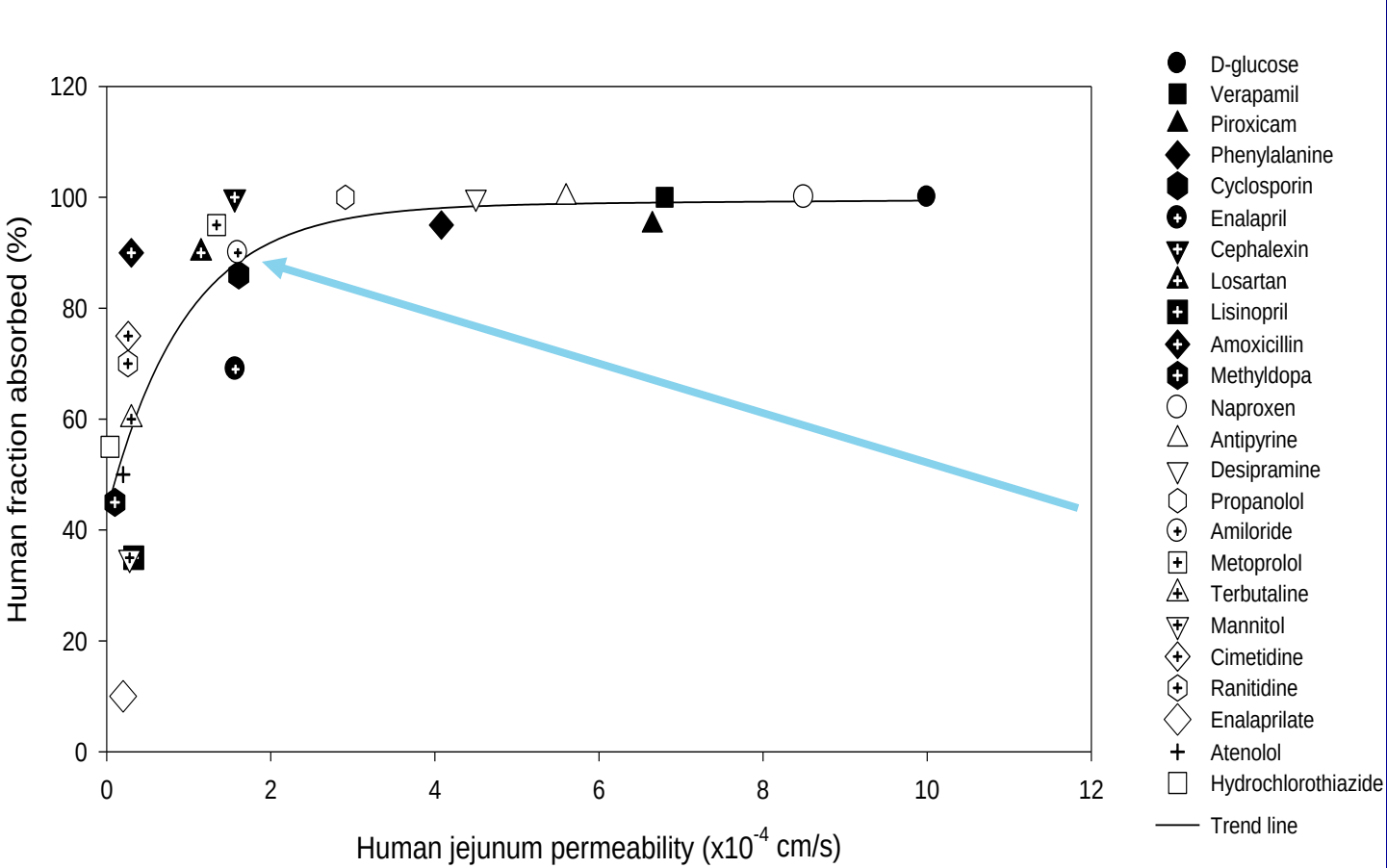


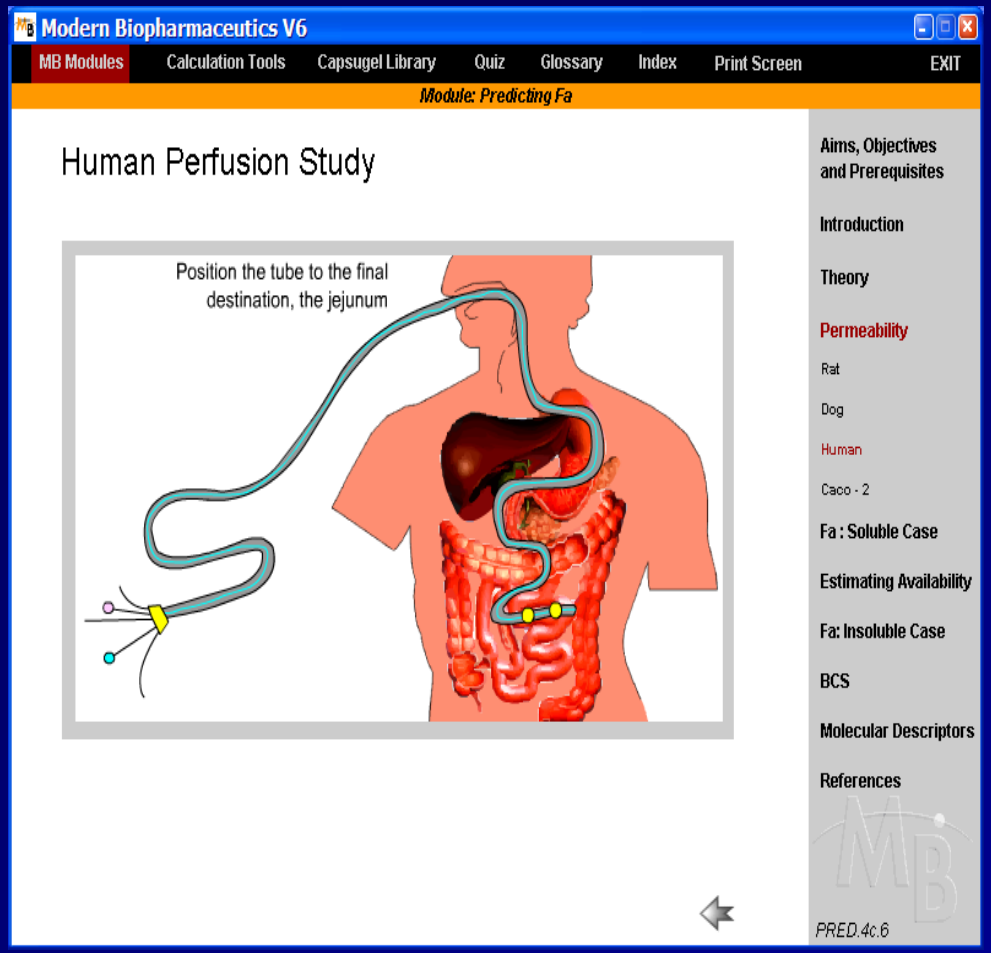
Figure 2. Human *in vivo* permeability values (P_{eff}) were determined by the use of a single-pass perfusion technique (Loc-I-Gut) in human jejunum. These human P_{eff} have been correlated to the fraction dose absorbed (f_a) of oral doses for a large number of drugs from different pharmacological classes which consequently represent structural diversity. Human *in vivo* jejunal permeability values for 42 compounds (31 drugs) were determined over a period of 18 years by applying this clinical technique and are presented in Tables I and II (Lennernas et al. 1992, 1993, 1994, 1997a, 2002b; Fagerholm et al. 1995, 1996, 1997, 1999; Lindahl et al. 1996; Lennernas 1997, 1998; Soderholm et al. 1997; Takamatsu et al. 1997, 2001; Sandstrom et al. 1998b, 1999b; Winiwarter et al. 1998, 2003; Sun et al. 2002; Chiu et al. 2003; Perri et al. 2003, 2006b; Tannergren et al. 2003a, b, 2004).

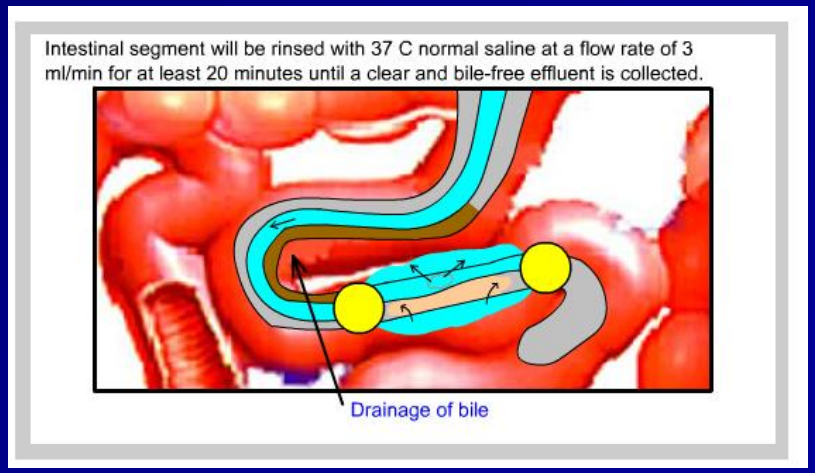
Human Fraction Absorbed vs. Jejunal Permeability pH=6.5



Sun et.al *Pharm. Res.* 19, 1400, 2002

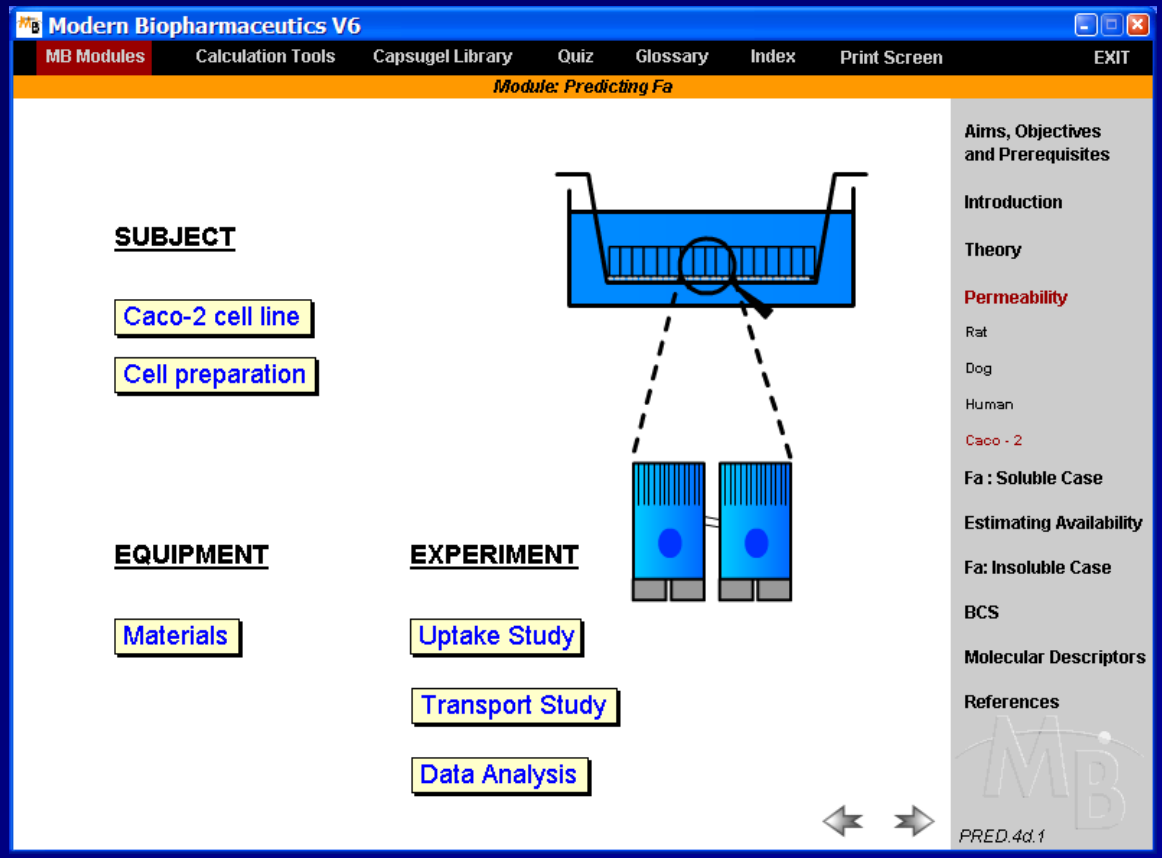
Human Permeability



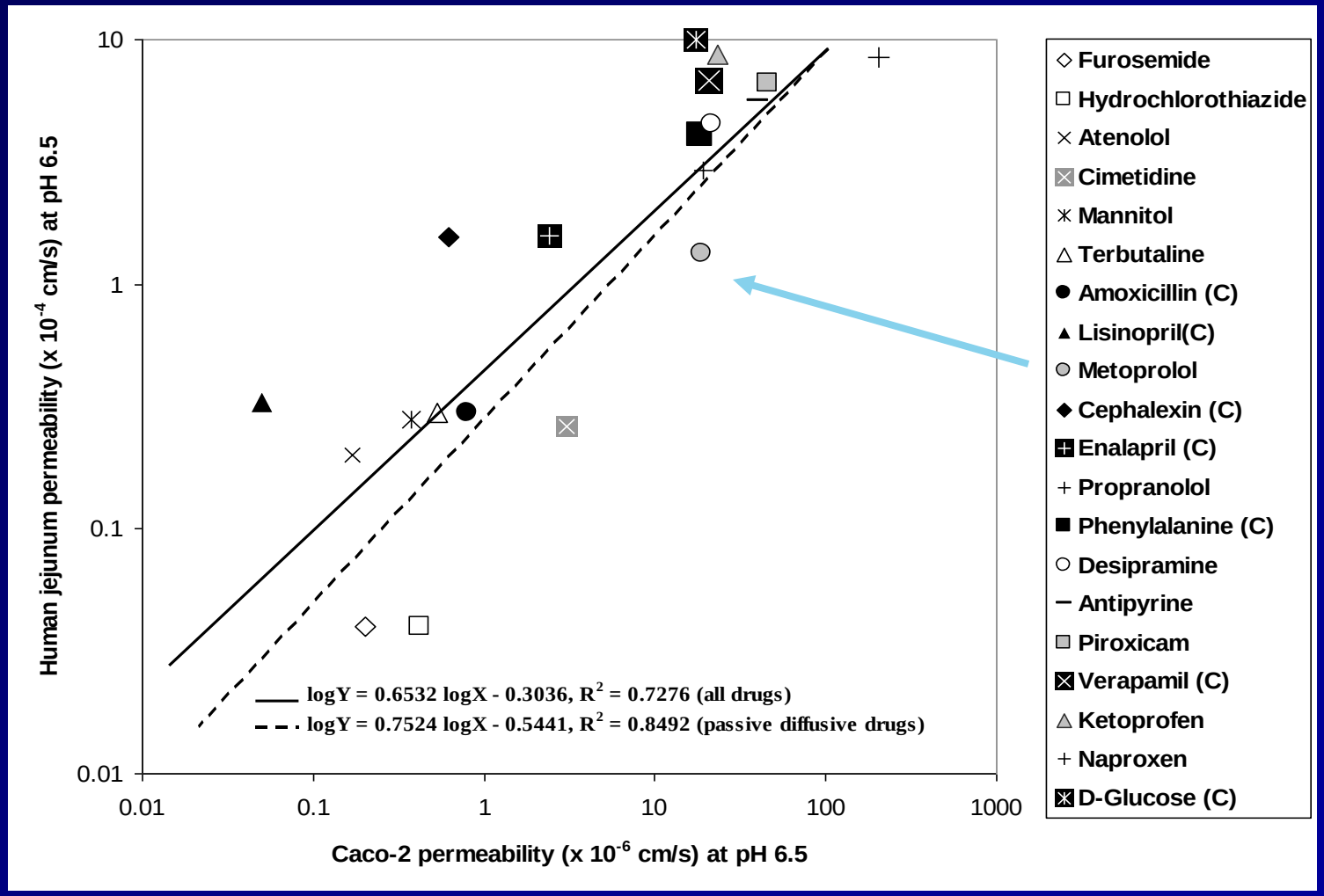


N. Takamatsu, et al. Pharm.Res., 14, 1127 (1997).

Tissue Culture Permeability



Human Caco-2 Permeability Correlation



‘In Silico’ (Computational)

molecular pharmaceutics

articles

A Provisional Biopharmaceutical Classification of the Top 200 Oral Drug Products in the United States, Great Britain, Spain, and Japan

Toshihide Takagi,[†] Chandrasekharan Ramachandran,[†] Maximal Bermejo,[‡] Shinji Yamashita,[§] Lawrence X. Yu,[⊥,*] and Gordon L. Amidon*[,†]

College of Pharmacy, University of Michigan, Ann Arbor, Michigan 48109-1065, Department of Pharmacy and Technology, University of Valencia, Valencia, Spain, Faculty of Pharmaceutical Sciences, Setsunan University, Osaka, Japan, and Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland 20857

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Abstract: Orally administered, immediate-release (IR) drug products in the top 200 drug product lists from the United States (US), Great Britain (GB), Spain (ES), and Japan (JP) were provisionally classified based on the Biopharmaceutics Classification System (BCS). The provisional classification is based on the aqueous solubility of the drugs reported in readily available reference literature and a correlation of human intestinal membrane permeability for a set of 29 reference drugs with their calculated partition coefficients. Oral IR drug products constituted more that 50% of the top 200 drug products on all four lists, and ranged from 102 to 113 in number. Drugs with dose numbers less than or equal to unity are defined as high-solubility drugs. More than 50% of the oral IR drug products on each list were determined to be high-solubility drugs (55−59%). The provisional classification of permeability is based on correlations of the human intestinal permeabilities of 29 reference drugs with the calculated Log *P* or CLogP lipophilicity values for the uncharged chemical form. The Log *P* and CLogP estimates were linearly correlated (r^2 = 0.79) for 187 drugs. Metoprolol was chosen as the reference compound for permeability and Log *P* or CLogP. A total of 62−69.0% and 56−60% of the drugs on the four lists exhibited CLogP and Log *P* estimates, respectively, greater than or equal to the corresponding metoprolol value and are provisionally classified as high-permeability drugs. We have compared the BCS classification in this study with the recently proposed BDDCS classification based on fraction dose metabolism. Although the two approaches are based on different in vivo processes, fraction dose metabolized and fraction dose absorbed are highly correlated and, while depending on the choice of reference drug for permeability classification, e.g., metoprolol vs cimetidine or atenolol, show excellent agreement in drug classification. In summary, more than 55% of the drug products were classified as high-solubility (Class 1 and Class 3) drugs in the four lists, suggesting that in vivo bioequivalence (BE) may be assured with a less expensive and more easily implemented in vitro dissolution test.

Keywords: BCS; solubility; dose number; permeability; partition coefficient; WHO essential drugs; top-selling US, European, Japanese drugs; BDDCS

Introduction

In vitro bioequivalence (BE) tests are the accepted standard for ensuring the therapeutic performance of drug products following manufacturing changes and for approval of generic drug product efficacy claims. BE standards are based on ensuring that reference and test products produce the same plasma concentration−time profiles through demonstrated statistical equivalence of C_{max} and AUC. While the in vivo BE test has been the norm for the past three decades, recently

* To whom correspondence should be addressed. Mailing address: College of Pharmacy, University of Michigan, 428 Church St., Ann Arbor, MI 48109-1065. Tel: (734) 764-2440. Fax: (734) 763-6423. E-mail: glamidon@umich.edu.
† University of Michigan.
‡ University of Valencia.
§ Setsunan University.
⊥ Food and Drug Administration.

▲ The opinions expressed in this report are those of the author and do not necessarily represent the views or policies of the Food and Drug Administration.

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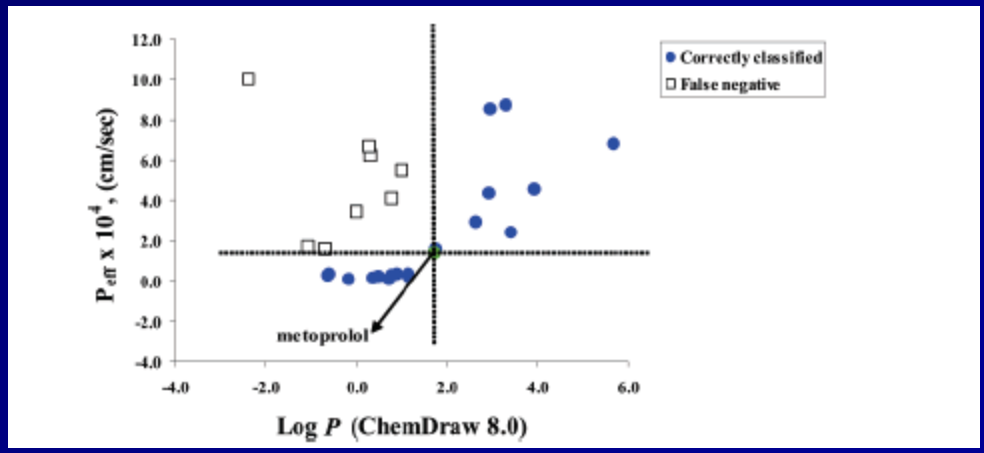
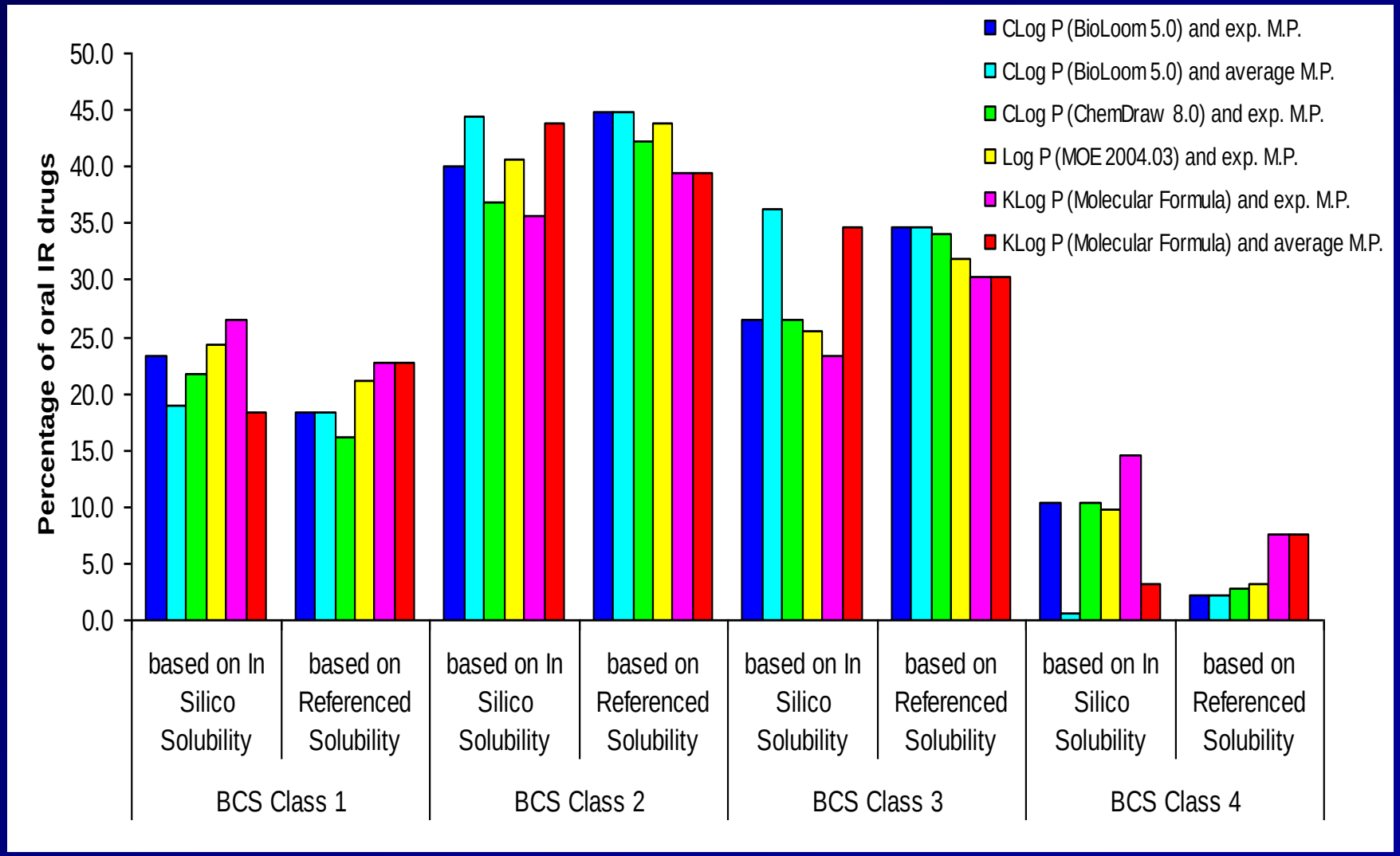


Drug database of oral immediate-release (IR) drugs on 200 top-selling US, GB, ES, JP, and KR drug products

- US: 113 oral IR drugs (56.5%)
- GB: 102 oral drugs (51.0%)
- ES: 106 oral drugs (53.0%)
- JP: 113 oral drugs (56.5%)
- KR: 87 oral drugs (43.5%)
- Based on 200 top-selling drug products in 5 countries, and WHO Essential drugs, drug databases of Combined List (346 drugs), Western List (147 drugs), Eastern List (163 drugs) was made and analyzed on molecular properties and BCS classification.

Comparison of the provisional BCS classification of *in silico* vs. referenced solubility approaches on 185 oral IR drugs



BCS and Dissolution: The Future

- Oral BE is a scientific question of ***in vivo*** Dissolution
- The *in vivo* Dissolution System (Gastrointestinal Tract) is complex
- We need to establish *in vitro* Dissolution Systems
- Need to Develop: **Bioperformance Dissolution Methods (BDM)**

BE Dissolution Proposal (Starting Point)

BCS Class	Drug Solubility pH 1.2	Drug Solubility pH 6.8	Drug Permeability	Preferred Procedure
I	High	High	High	>85% Dissolution in 15 min; 30 min, f2., pH = 6.8.
II-A	Low	High	High	15 min at pH=1.2, then 85% Dissolution in 30 min., pH = 6.8; F2>50; 5 points minimum; not more than one point > 85%.
II-B	High	Low	High	>85% Dissolution in 15 min., pH = 1.2.
II-C	Low	Low	High	15 min at pH=1.2; then 85% Dissolution in 30 min., pH = 6.8 plus surfactant*; F2>50; 5 points minimum, not more than one point > 85%.
III	High	High	Low	>85% Dissolution in 15 min., pH = 1.2, 4.5, 6.8.
IV-A	Low	High	Low	15 min. at pH = 1.2; then 85% Dissolution in 30 min., pH = 6.8,; F2>50; 5 points minimum.; not more than one point > 85%.
IV-B	High	Low	Low	>85% Dissolution in 15 min., pH = 1.2.
IV-C	Low	Low	Low	15 min at pH=1.2; then 85% Dissolution in 30 min., pH = 6.8 plus surfactant*; F2>50; 5 points minimum, not more than one point > 85%.

BCS Dissolution Proposal

- This is too much to digest in one seminar
- The USP can not do this because of it's charter
- The FDA can not do this because of the legal basis for proprietary information
- This is how we do business (develop products)

BCS and Dissolution Conclusions

- New BE Paradigm
- Reduce Unnecessary *In Vivo* Studies
- Increase Oral Product Quality
- Based on Scientific Principles and Extendable
  - E.g. Food Effects
- It is up to us!