GDUFA Regulatory Science Initiatives:

Public Workshop for 2019 Generic Drug Research

May 24, 2018
FDA White Oak Campus,
Silver Spring, MD

Individual Physiology, Biology, Anatomy and Their Interplay with Formulation:

Impossible Permutations of Conditions to be Studied for Bioequivalence

Amin Rostami

Professor of Systems Pharmacology
University of Manchester, UK
&
Chief Scientific Officer & Senior Vice President of R&D
Certara , Princeton, USA

BE & Me: Going Long way Back!

Sensitivity of Indirect Metrics for Assessing "Rate" in Bioequivalence Studies—Moving the "Goalposts" or Changing the "Game"

AMIN ROSTAMI-HODJEGAN, PETER R. JACKSON, AND GEOFFREY T. TUCKER[x]

J Pharm Sci 1994

- Discussing the ambiguities related to assurance of pharmaceutical quality vs clinical safety and efficacy
- Advocating for indirect measures of safety and efficacy

Main goals of the workshop:

- To identify research that will be relevant to the generic industry as they attempt to develop "substitutable generic products" by the choice or the most informative BE studies
- To provide ideas on alternatives to *in vivo* studies that are not informative
- To offer approaches in assessing and identifying potential problems with substitution that may occur in different patient groups

Past, Present and Future of Bioequivalence: Improving the Assessment and Extrapolation of Therapeutic Equivalence

RODRIGO CRISTOFOLETTI, MALCOLM ROWLAND, LAWRENCE J LESKO, HENNING BLUME, AMIN ROSTAMI-HODJEGAN, JENNIFER B DRESSMAN

J Pharm Sci 2019 (Under Review)

- Systems approach has created a paradigm shift such that instead of relying extensively on end product testing and one-size-fits-all regulatory criteria, focus is on building quality into the product by design as well as fostering product specific clinically relevant specifications.

- Evolution of bioequivalence regulations shows a trajectory towards applying a Bayesian-like approach, and considering all relevant prior knowledge, to guide decisions in a patient-centric environment.

Missing “Patient” Element from the Start

The first US legal definitions of BA and BE were stated in the Code of Federal Regulation 21CFR320.1. For systemically acting drugs,

BA was defined in the Act as

“the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action”

... and BE as

“the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study”

Open Questions – Possible Answers

1. Can BE for two formulations be established in healthy volunteers and yet there is no BE in patient populations?
   YES IT CAN BE THE CASE

2. Do we need to conduct BE in the patient populations?
   NOT NECESSARILY

3. How do we refute the likelihood of difference in BE status between healthy volunteers and patients?
   VIA VIRTUAL CLINICAL STUDIES

4. How reliable – qualified are these Virtual Studies?
   ALL DEPENDS ON DATA THAT INFORMS THE POPULATION AND VERIFICATION OF PREVIOUS CASES

Variability & Me: Untold Story of New IVIVE-PBPK!

Eur J Clin Pharmacol (1999) 55: 559–565

SPECIAL ARTICLE

J. C. Krayenbühl · S. Vozeh
M. Kondo-Oestreicher · P. Dayer

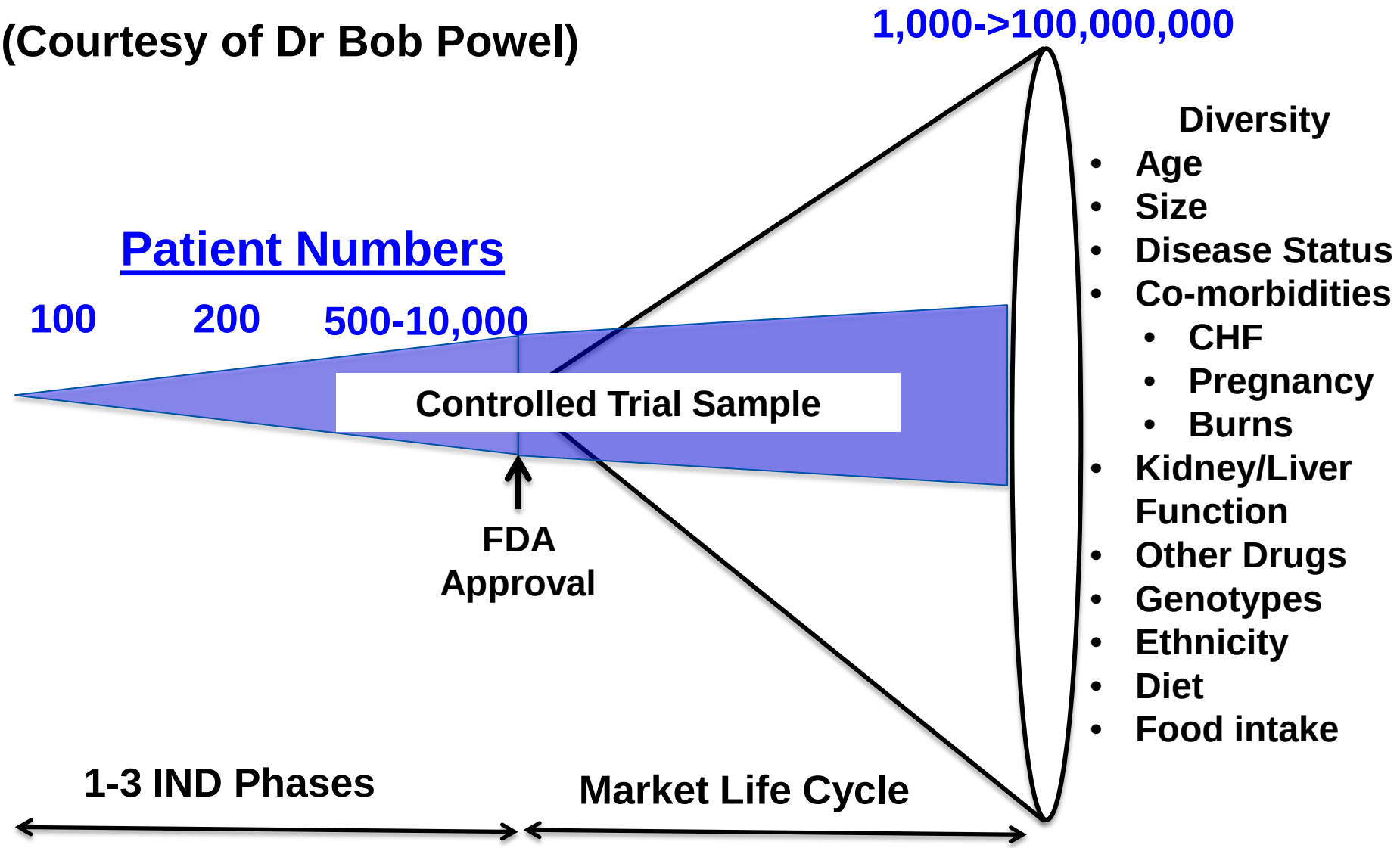
Drug–drug interactions of new active substances: mibefradil example

J.C. Krayenbühl · S. Vozeh
Swiss Intercantonal Office for the Control of Medicines,
Berne, Switzerland

Interpretation of interaction studies should focus **not** only on mean effect but also the observed and ***theoretically conceivable extremes.***

Efficacy-Safety Evidence Gap Over Time: Even for New Drugs

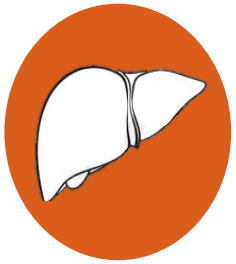
(Courtesy of Dr Bob Powel)



http://www.nationalacademies.org/hmd/Reports/2017/drug-development-paradigm-in-oncology-proceedings.aspx

Real People Are Made of “INTERACTING COVARIATES”

Intrinsic Factors



Hepatic Impairment

Renal Impairment

Bariatric Surgery & Obesity

Pregnancy

Ethnicity & Genetics

Pediatrics

Cancer

Extrinsic Factors

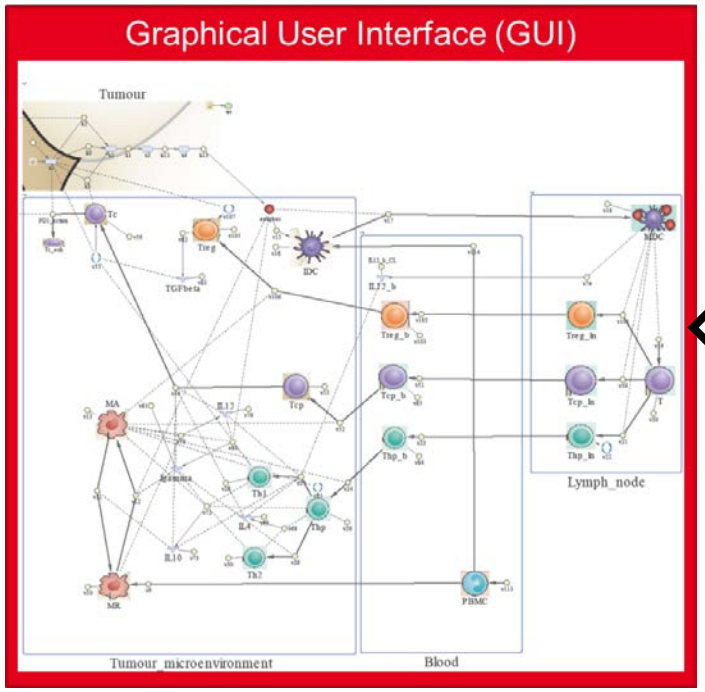
Smoking

Alcohol

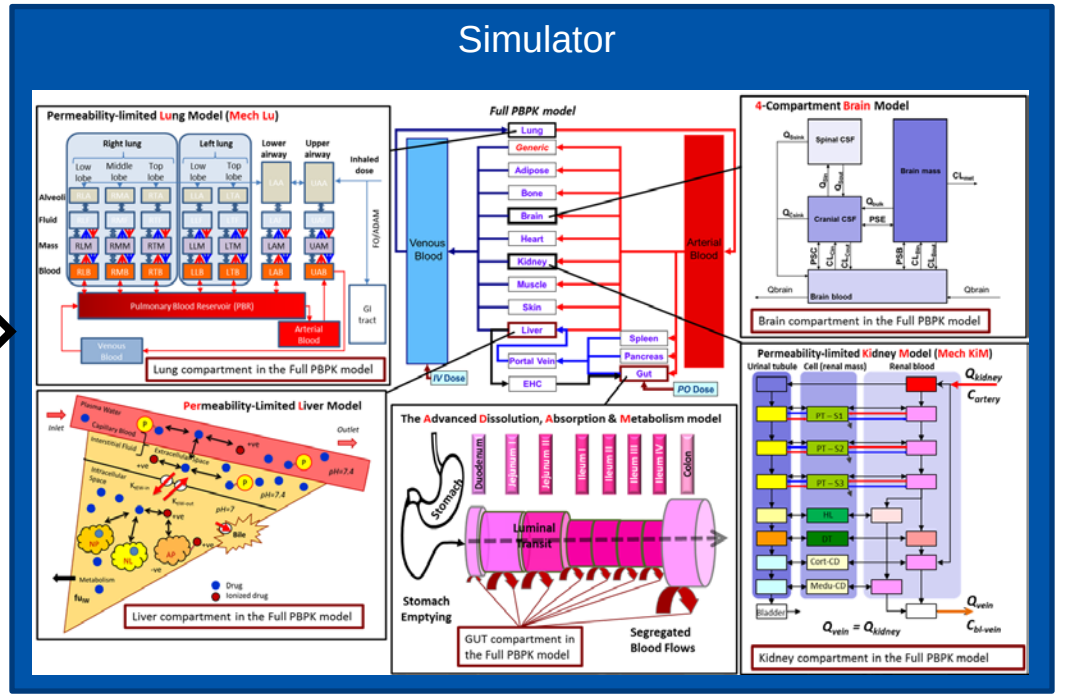
Diet

Polypharmacy/ Drug-drug Interactions

Sub-Models within PBPK and Link to QSP



Immuno-Oncology (IO) or
Immuno-Genicity (IG) Model

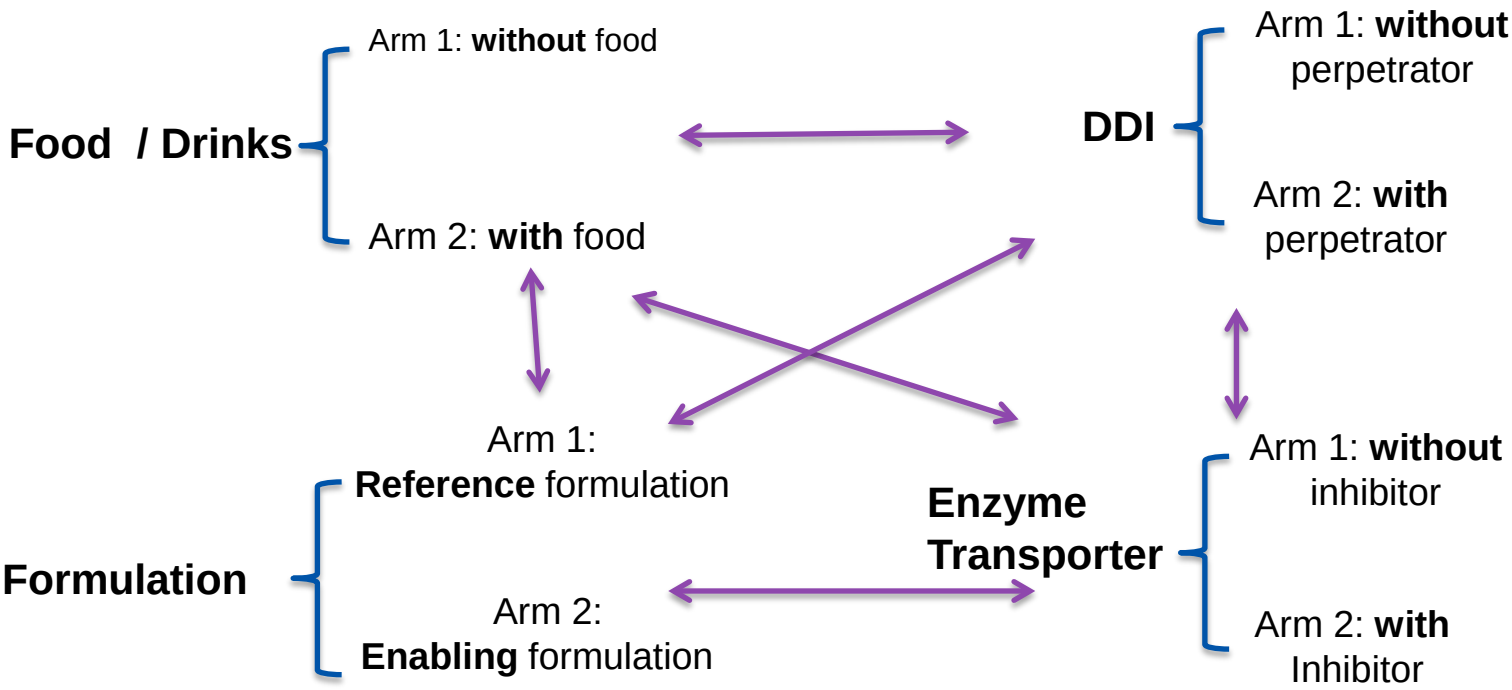


Full range of PBPK sub-models involving GI Tract, Liver, Skin, Kidney, Brain, …

The Task is Not Just About Models:

- **Obtaining reliable POPULATION DATA for biological, patho-physiological and anatomical attributes is essential.**

Impossible Task of Investigating the Multiple Factors Which May Affect BE



Number of arms = Levels^{effects}

Even in the simplest case of two level (High and Low) = 16

Contents lists available at ScienceDirect

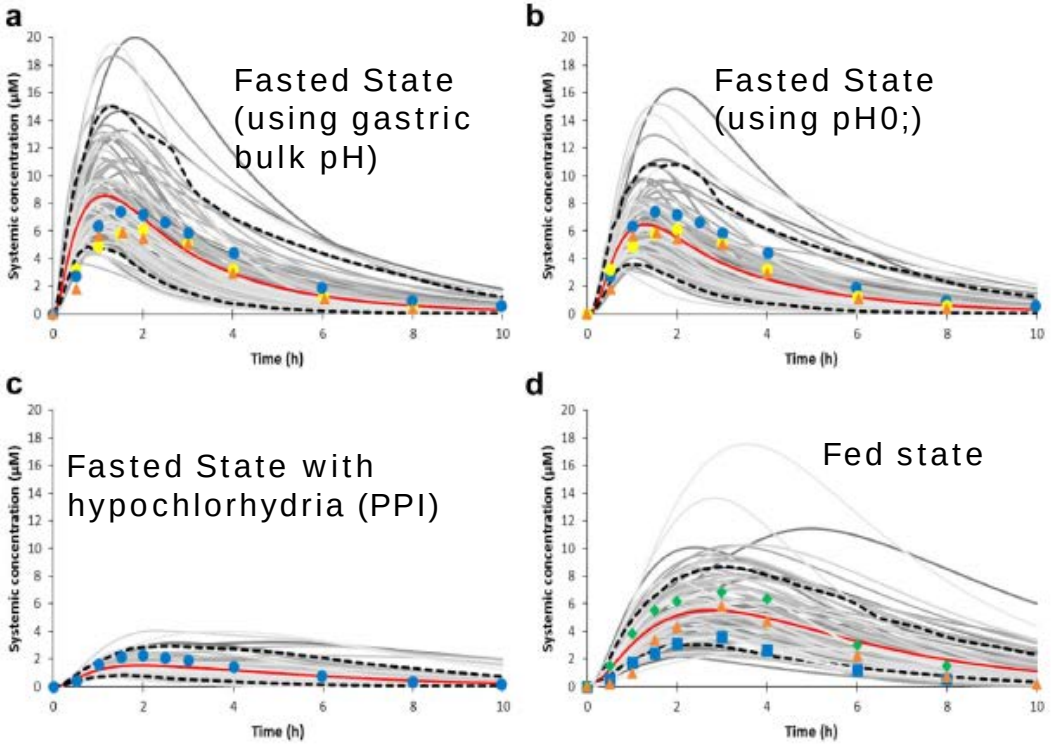
Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Assessment of Bioequivalence of Weak Base Formulations Under Various Dosing Conditions Using Physiologically Based Pharmacokinetic Simulations in Virtual Populations. Case Examples: Ketoconazole and Posaconazole

Rodrigo Cristofoletti [1,2], Nikunikumar Patel [3], Jennifer B. Dressman [2,*]



Formulation-Dependent Dissolution in Stomach:

- Might not be important for BE of one drug but may affect another.
- BE in healthy volunteers might be the same but not in patient groups taking PPI

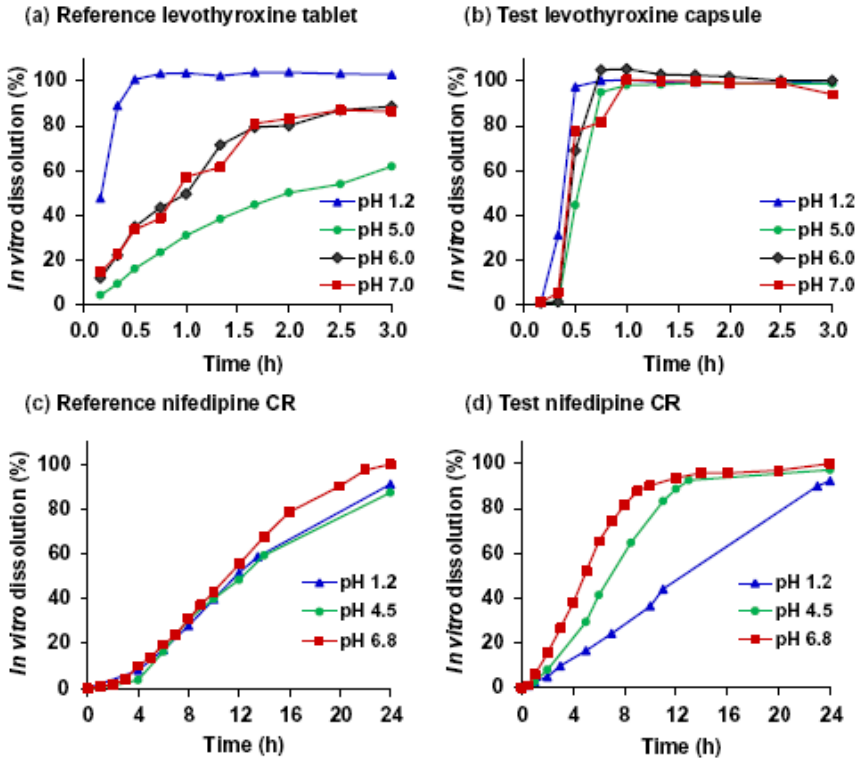
Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Virtual bioequivalence for achlorhydric subjects: The use of PBPK modelling to assess the formulation-dependent effect of achlorhydria

Kosuke Doki[a,b,*], Adam S. Darwich[a], Nikunjkumar Patel[c], Amin Rostami-Hodjegan[a,c]



Formulation-Dependent Dissolution in Stomach:

- BE in healthy young Caucasian volunteers might be the same but not in patient groups belonging to older age in a different ethnic group

BE Formulations may have different DDI Profile

Victim (CYP3A substrate)	Posaconazole	
	Oral suspension	D-tablets
Sirolimus (Trough conc./dose ratio)	2.7 fold (400 mg bid/200 mg tid)	5.8 – 8.5 fold (300 mg qd, N=1)
Sirolimus (AUC ratio)	8.3-fold (400 mg bid)	Not reported
Midazolam, po (AUC ratio)	4.4-fold (200 mg bid) 4.8-fold (400 mg bid)	Not reported

formulation effect ?

Takanobu Matsuzuki et al (under preparation)

BIOPHARMACEUTICS & DRUG DISPOSITION
Biopharm. Drug Dispos. 38: 260–270 (2017)
Published online 14 February 2017 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/bdd.2058

The absorption kinetics of ketoconazole plays a major role in explaining the reported variability in the level of interaction with midazolam: Interplay between formulation and inhibition of gut wall and liver metabolism

Bo Liu[a], H. Kim Crewe[a], Mahmut Ozdemir[b], Karen Rowland Yeo[a], Geoffrey Tucker[c], and Amin Rostami-Hodjegan[a,d,*]

What is the Clinical Relevance of BE in the Relevant Population

Original Investigation

AJKD

Results of ASERTAA, a Randomized Prospective Crossover Pharmacogenetic Study of Immediate-Release Versus Extended-Release Tacrolimus in African American Kidney Transplant Recipients

Jennifer Trofe-Clark, Daniel C. Brennan, Patricia West-Thielke, Michael C. Milone, Mary Ann Lim, Robin Neubauer, Vincenza Nigro, and Roy D. Bloom

- There were no significant differences in $AUC_{0\text{-}24}$ or C_{min} between CYP3A5 expressers and nonexpressers during administration of either IR- or CR.
- With IR, tacrolimus C_{max} was 33% higher in CYP3A5 expressers compared with nonexpressers (P = 0.04) ; With CR, this difference was only 11% (P = 0.4).
- Achieving therapeutic tacrolimus trough concentrations with IR in most African Americans results in significantly higher peak concentrations, potentially magnifying the risk for toxicity and adverse outcomes. This PGx effect is attenuated by delayed tacrolimus absorption with CR.

Tacrolimus Formulations and African American Kidney Transplant Recipients: When Do Details Matter?

Dirk R.J. Kuypers

- The effects of CYP3A5 on conventional twice-daily tacrolimus (IR) and extended-release once-daily tacrolimus (ER) formulations in terms of exposure, dose requirements, and dose conversion ratios are well established in ***whites***.

- A randomized prospective study in which most participants were ***white*** demonstrated no clinical benefit of CYP3A5 genotype–based IR dosing in de novo kidney transplantation

- The bioavailability of the different tacrolimus formulations has not been formally
- evaluated in ***African Amer***ican kidnet transplant revipients.

- Trofe-Clark et al showed in a prospective randomized comparative crossover pharmacokinetic study (ASERTAA [A Study of Extended Release Tacrolimus in African Americans]) that achieving therapeutic trough concentrations with IR in CYP3A5-expressing ***African American*** patients was accompanied by significantly
- higher peak concentrations (Cmax), an effect that was attenuated when using the CR formulation.

Could have we predicted this? Possibly yes!

European Journal of Pharmaceutical Sciences 67 (2015) 32–44

Contents lists available at ScienceDirect

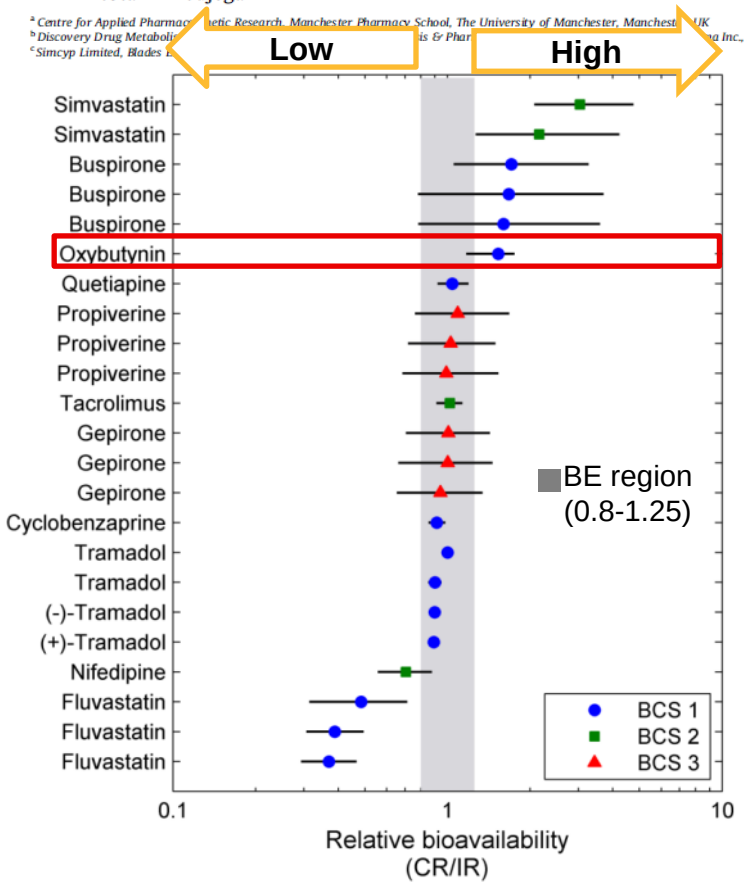
European Journal of Pharmaceutical Sciences

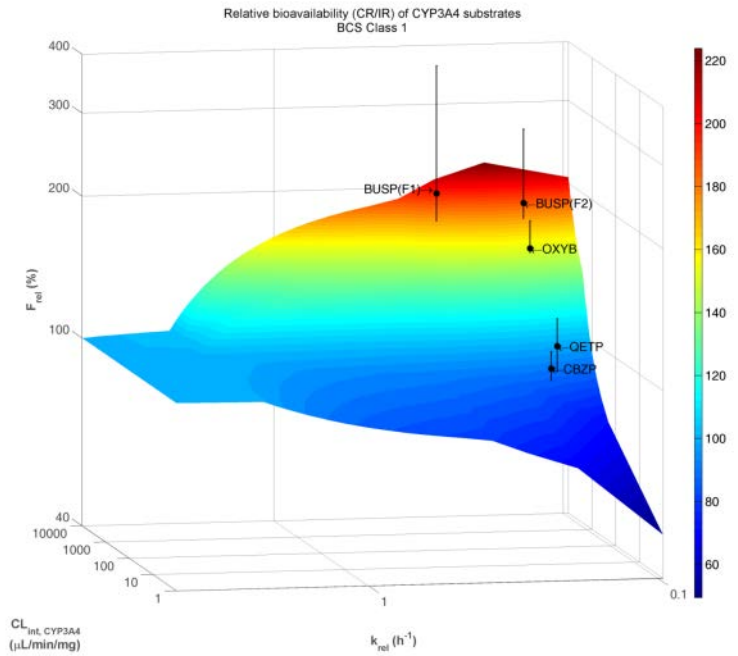
journal homepage: www.elsevier.com/locate/ejps

Analysis of the impact of controlled release formulations on oral drug absorption, gut wall metabolism and relative bioavailability of CYP3A substrates using a physiologically-based pharmacokinetic model

Andrés Olivares-Morales [a], Yoshiteru Kamiyama [a,b], Adam S. Darwich [a], Leon Aarons [a], Amin Rostami-Hodjegan [a,c,*]

[a] Centre for Applied Pharmacokinetic Research, Manchester Pharmacy School, The University of Manchester, Manchester, UK
[b] Discovery Drug Metabolism & Pharmacokinetics, Astellas Pharma Inc., Ibaraki, Japan
[c] Simcyp Limited, Blades Enterprise Centre, John Street, Sheffield, UK





The AAPS Journal (© 2015)
DOI: 10.1208/s12248-015-9758-0

Research Article

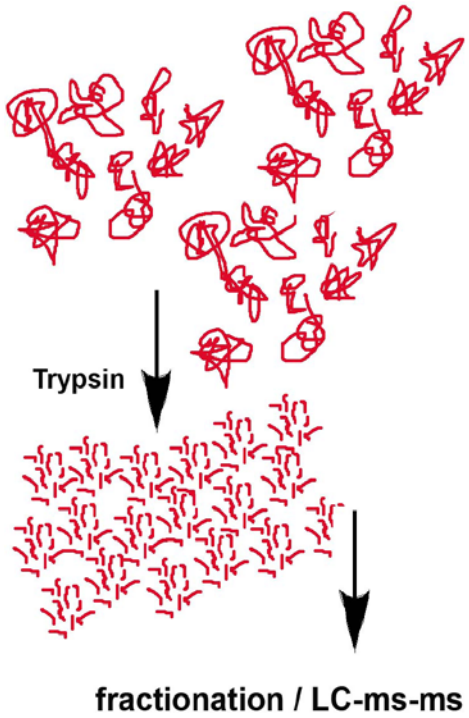
Translating Human Effective Jejunal Intestinal Permeability to Surface-Dependent Intrinsic Permeability: a Pragmatic Method for a More Mechanistic Prediction of Regional Oral Drug Absorption

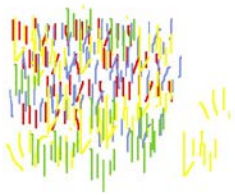
Andrés Olivares-Morales,[1] Hans Lennernäs,[2] Leon Aarons,[1] and Amin Rostami-Hodjegan[1,3,4]

[1]Olivares-Morales et al, 2015a,b

Filling the Gaps: Systems Information *vs* Drug

LCMS/MS Proteomics
of
Relevant Tissues
in
Relevant Patient Populations



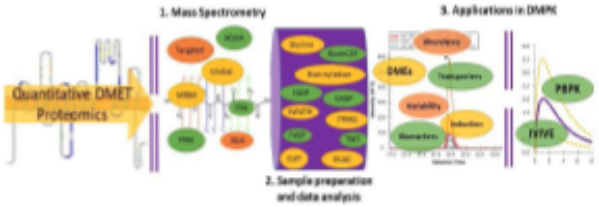


PRINT PAGE | SIG

ISSX Workshop on LC-MS Proteomics

Meetings » ISSX Workshop on LC-MS Proteomics

Towards Reaching a Consensus on Using Quantitative LC-MS/MS Proteomics in Translational DMPK/PD Research



September 27 & 28, 2018
Takeda Pharmaceuticals USA, Inc. Auditorium
Cambridge, Massachusetts, USA

Discussions & Debate