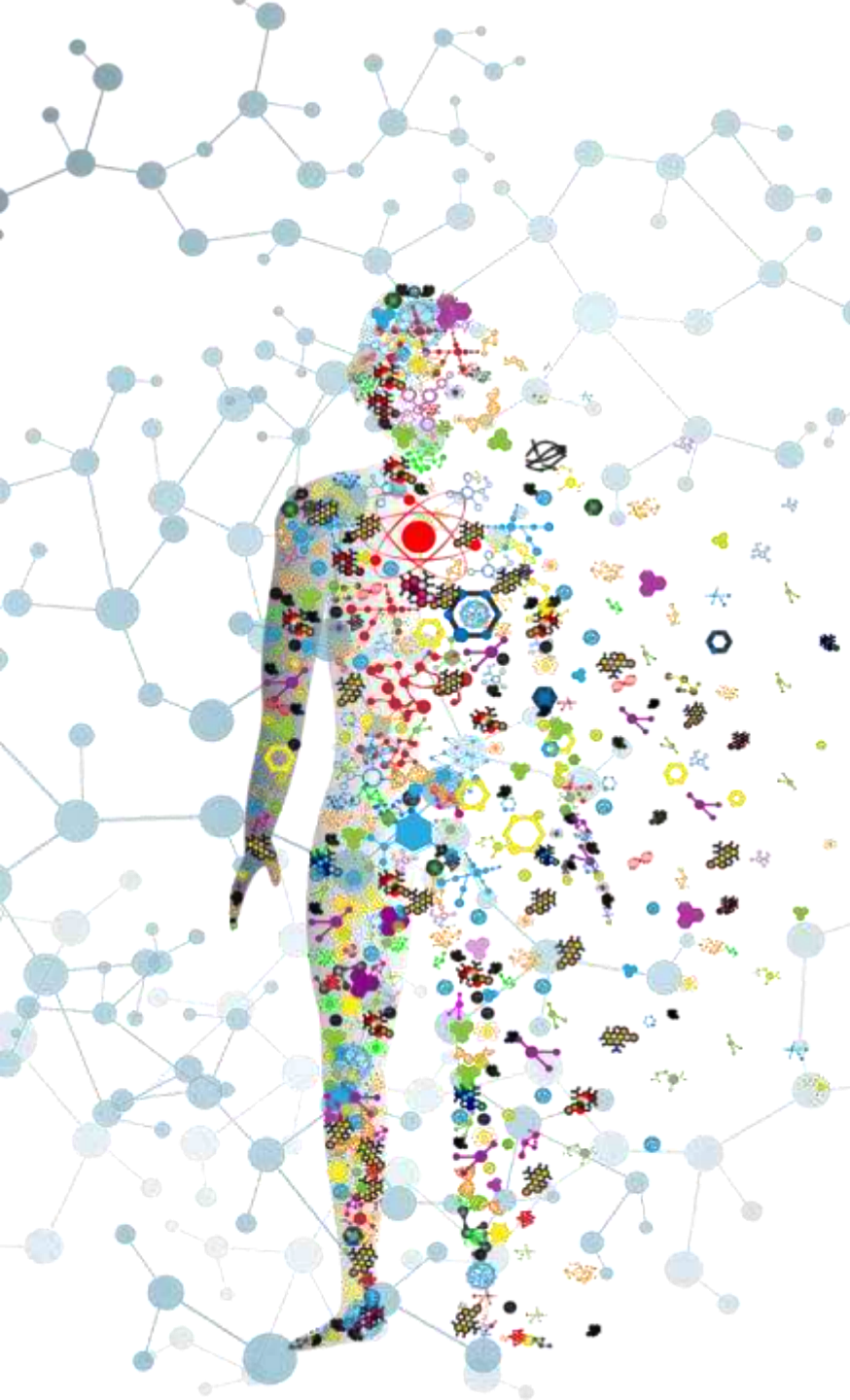


GDUFA Regulatory Science Initiatives - Virtual Public Workshop– 23rd June 2021
The 2022 Priorities for Generic Drug Research

Challenge #1:
Model-Integrated Evidence for Generic Drug Development

Community Trust in M&S
(Modelling & Simulation)

The Move from Scientific Curiosity to Ingrained Industrial Applications

Amin Rostami, PharmD, PhD., FCP, FJSSX, FAAPS, FBPS

Professor of Systems Pharmacology
Director of Centre for Applied Pharmacokinetics Research, University of Manchester, UK

Senior Vice-President of R&D and Chief Scientific Officer,
Certara, Princeton, USA

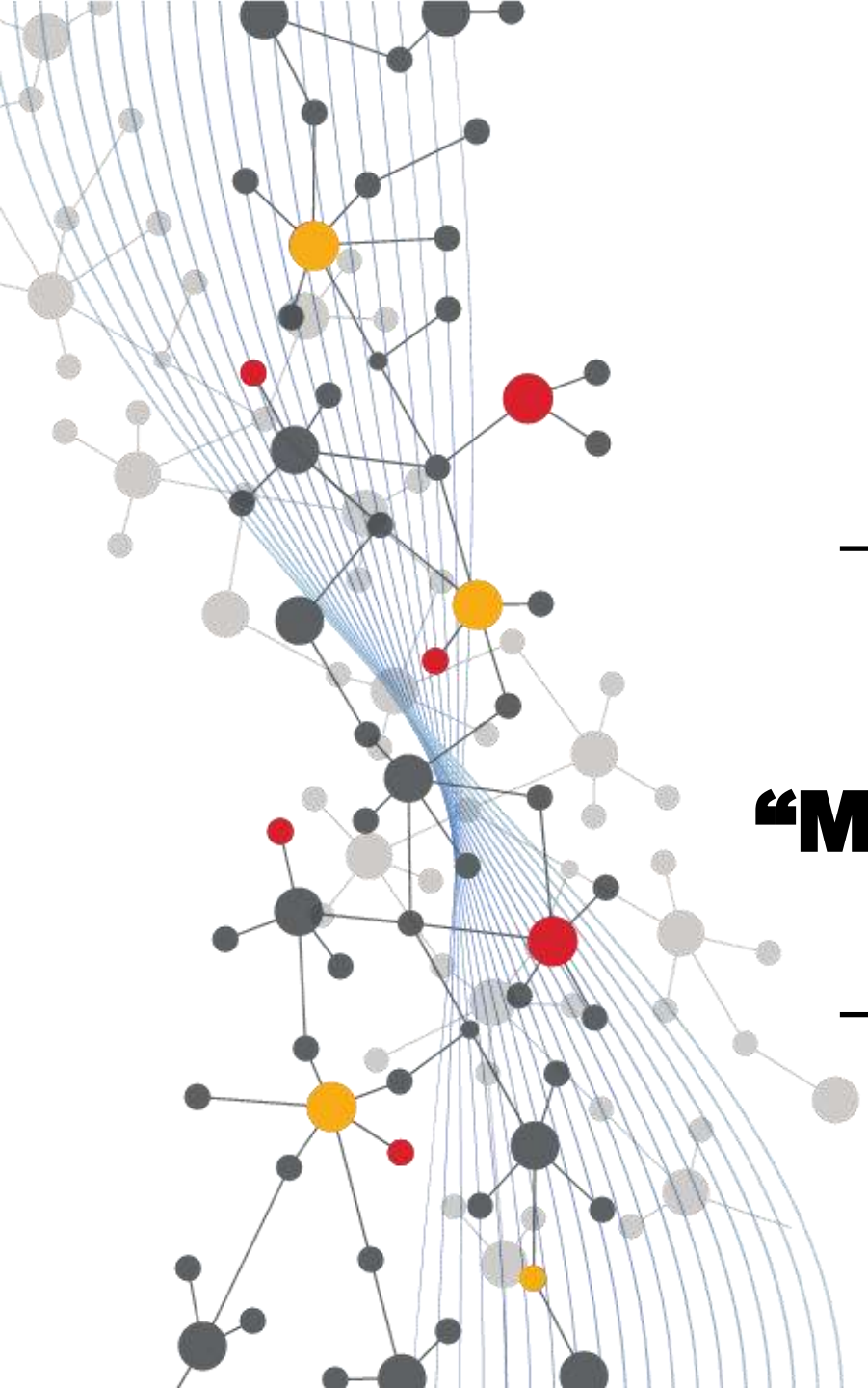
Declaration of Conflict of Interest

As the Director of CAPKR (Centre for Applied Pharmacokinetics Research my research is sponsored by a group of pharmaceutical companies (currently Merck, GSK, Eli Lily, Genentech, J&J, AbbVie, EMD Serono, Takeda) in addition to grants from non-for-profit organizations or government and research councils.

As the Chief Scientific Officer and SVP of R&D at Certara, I have been involved in overseeing the development of software tools which are used by a large group of pharmaceutical companies during drug discovery and development; particularly in the area of physiologically-based pharmacokinetics (PBPK) and quantitative systems pharmacology (QSP).

Disclaimer

This presentation is prepared in my *personal capacity* as a scientist engaged with pharmaceutical science for over 30 years. The opinions expressed herein are my own and do not reflect the views, policies, strategies of any of the organisations I am affiliated with.



Topic for the Next 7 Minutes

True:

"M&S Has Matured Enough!"

False:

"M&S Is Ingrained in Pharmaceutical Drug Development!"

VERTICAL *vs* LATERAL Development of M&S

Different Kind of Cars! ; Different Kind of Drivers!

Research Frontier

Scaling up

Routine Scaled Up Usage

***'Scaling'* M&S Requires Less than Racing Cars & Racing Car Drivers!**

Bespoke/Hand-Made vs Mass Produced

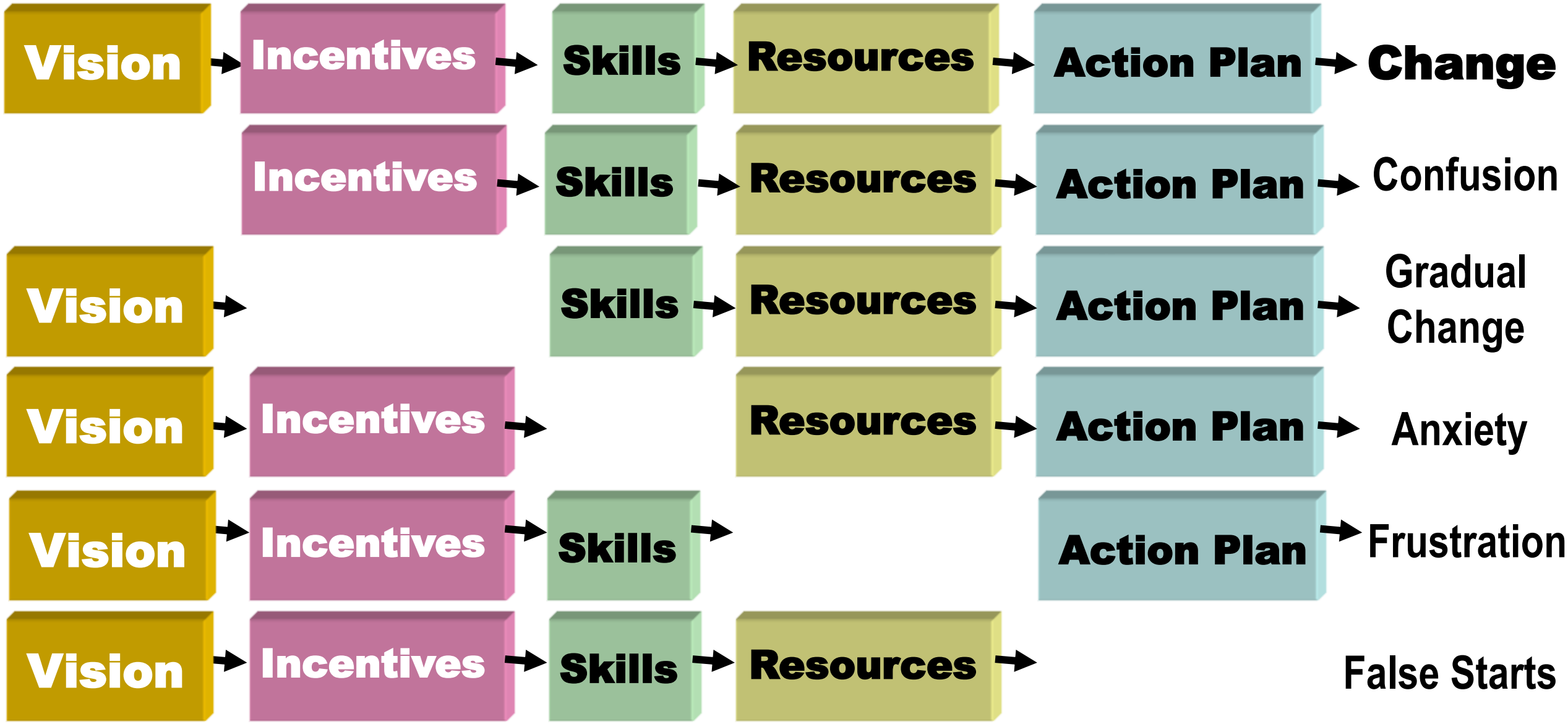
'Toys for Big Boys' vs 'Modelling for All'

'The Role of Professional M&S Tool Developers'?

"It is *Undeniable* Fact"
that:

User-Friendly (non-open-source/commercial) tools, with large database of systems parameters, and dedicated resources to educational needs of users, have played a *'significant'* role in expansion of Mechanistic Model Applications in NDA and IND procedures in drug development.

Management Issue & Not Just Science: Ingraining Translational M&S in Pharmaceutical Development



Courtesy of Dr Mark Holbrook (Senior Advisor, QSTS Team, Certara)

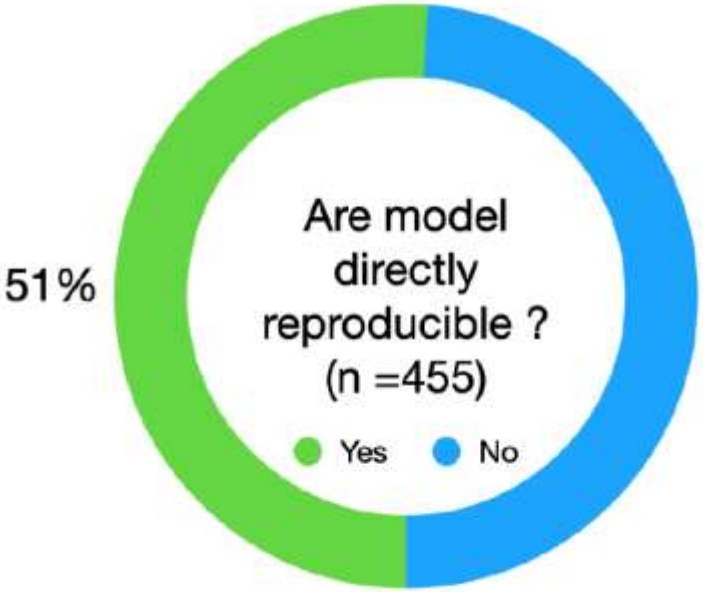
Altruistic but Naïve for Scaled Operations: Open Source-Code

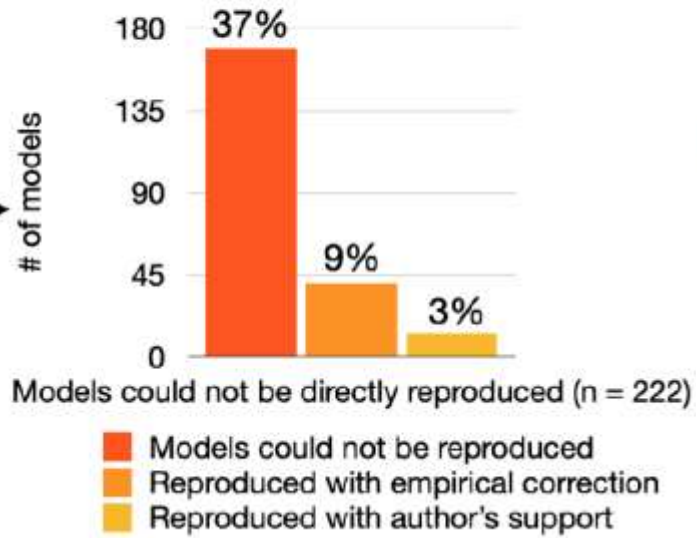
Reproducibility in systems biology modelling

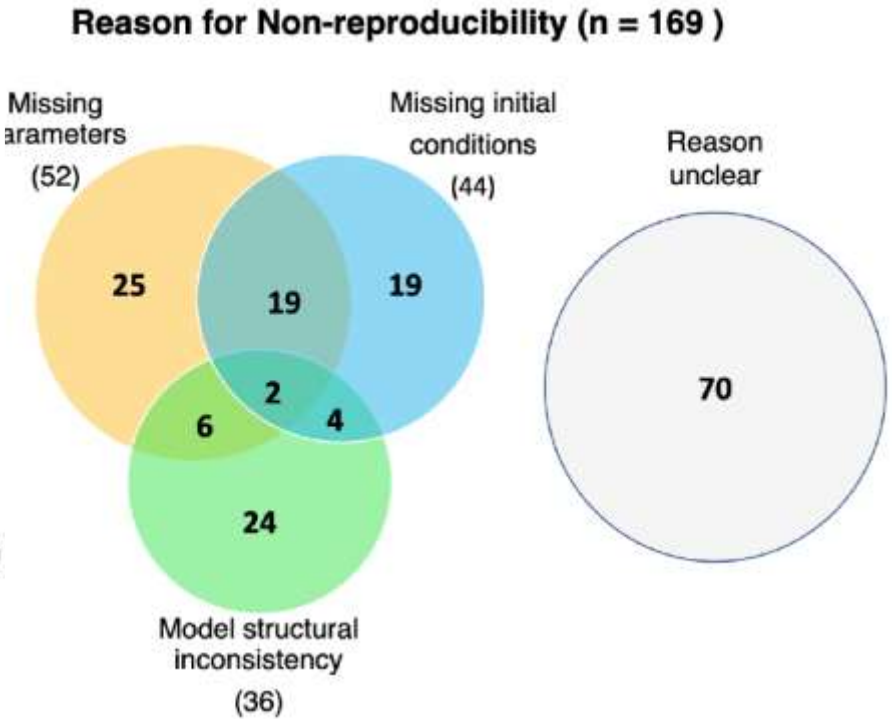
Krishna Tiwari[1,2], Sarubini Kananathan[1], Matthew G Roberts[1], Johannes P Meyer[1], Mohammad Umer Sharif Shohan[1], Ashley Xavier[1], Matthieu Maire[1], Ahmad Zyoud[1], Jinghao Men[1], Szeyi Ng[1], Tung V N Nguyen[1], Mihai Glont[1], Henning Hermjakob[1,3,*] & Rahuman S Malik-Sheriff[1,**]

molecular systems biology

DOI 10.15252/msb.20209982
Mol Syst Biol. (2021) 17: e9982





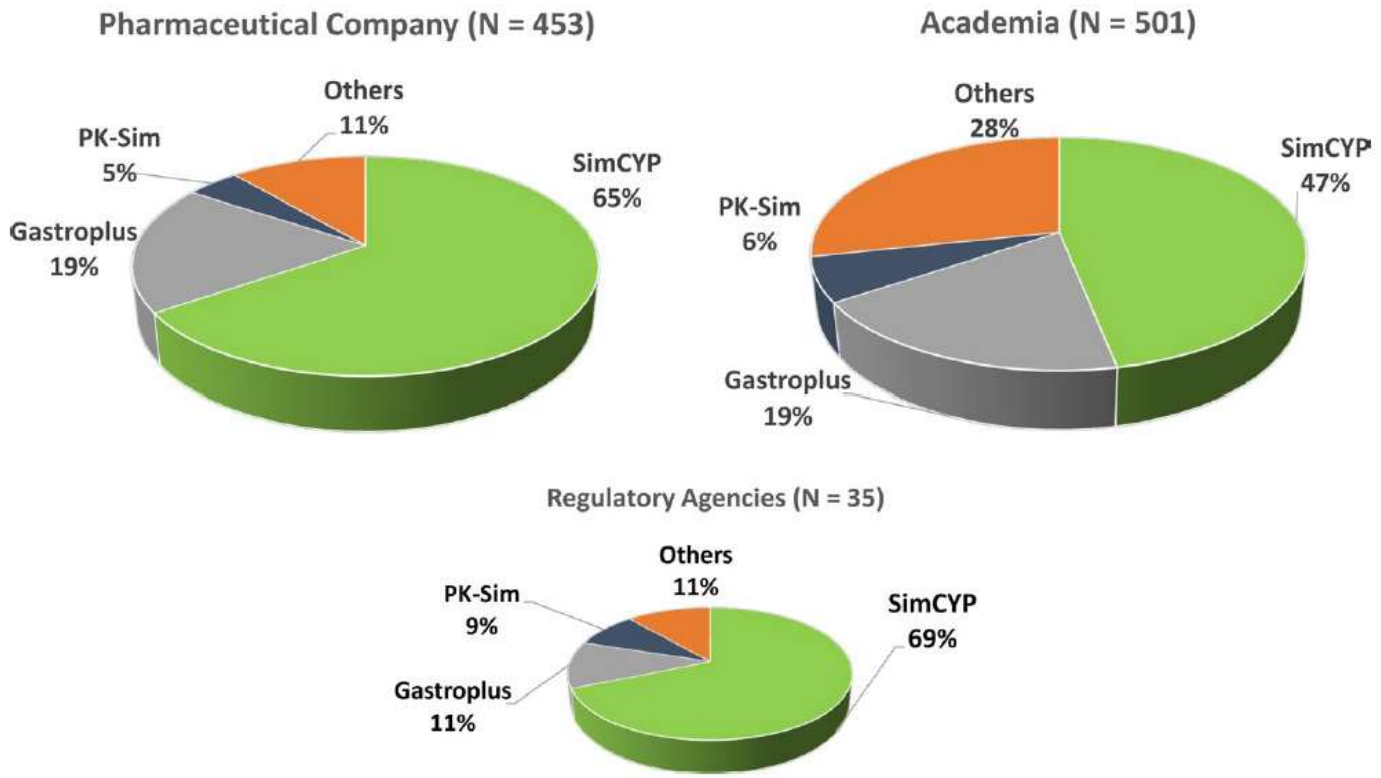


Opening a debate on open-source modeling tools: Pouring fuel on fire versus extinguishing the flare of a healthy debate

Amin Rostami-Hodjegan[1,2] | Frederic Y. Bois[2]

CPT Pharmacometrics Syst.Pharmacol. 2021;00:1–8.
https://doi.org/10.1002/psp4.12615

- Software/platform
- Computing/Program Language
- Model
- Data
- Open source
- Commercial Software
- Open Science
- Sponsors and Beneficiaries



Assessing 1000's Lines of Program for

Open Source-Code Models?

"An Imposiible Task"

Alternative Option:

"GLASS BOX"

Full Transparency

via
Peer Review by Experts,
Scientific Publications,
Public Workshops,
& Full Implementation Documents which Are Accessible to Regulators.
BUT,
Quality Assured
&
NOT *EVERYONE* CAN MODIFY THE CODE!

STATE OF THE ART

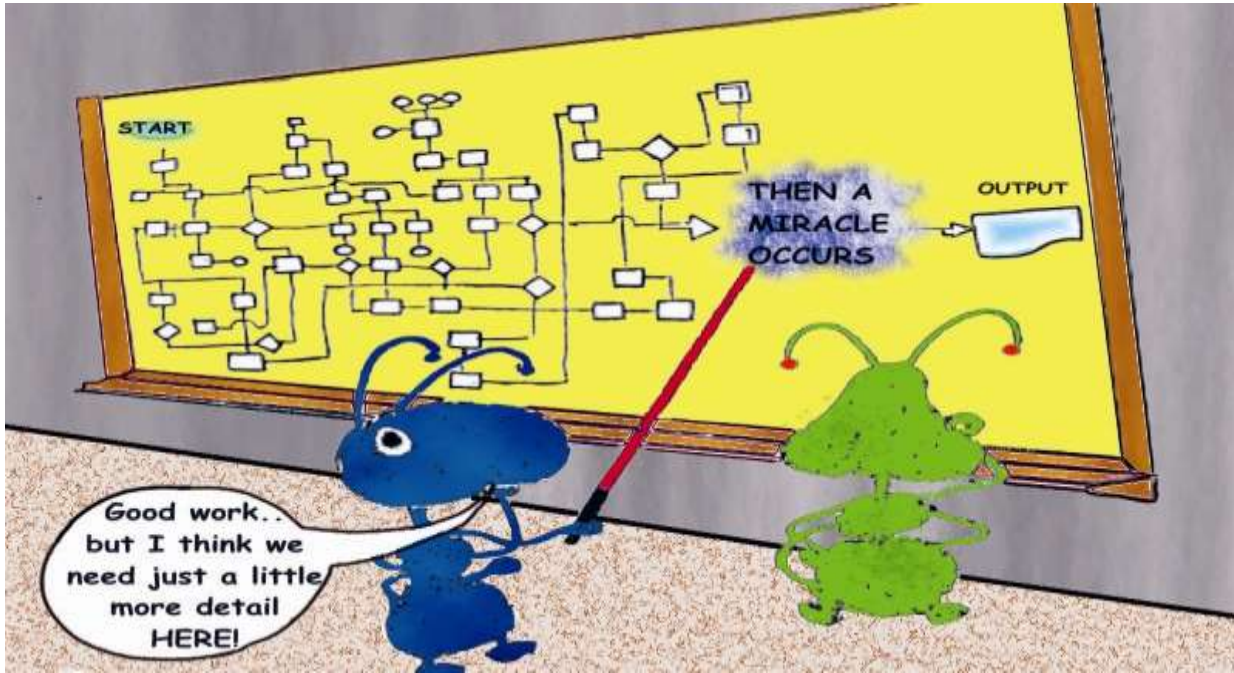
Reverse Translation in PBPK and QSP: Going Backwards in Order to Go Forward With Confidence

Amin Rostami-Hodjegan[1,2]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 103 NUMBER 2 | FEBRUARY 2018

NO TO

BLACK BOX



My Model? Your Model? His Model? Her Model? Whose Model?

ELSEVIER

European Journal of Pharmaceutical Sciences 17 (2002) 51–61

EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES

www.elsevier.nl/locate/ejps

Prediction of intestinal absorption: comparative assessment of GASTROPLUS™ and IDEA™

Neil Parrott*, Thierry Lavé

So Many Comparisons

So Little Insight!

ELSEVIER

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmacokinetics, Pharmacodynamics and Drug Transport and Metabolism

Prediction Characteristics of Oral Absorption Simulation Software Evaluated Using Structurally Diverse Low-Solubility Drugs

Check for updates

Naoya Matsumura [1,*], Shun Hayashi [2], Yoshiyuki Akiyama [3], Asami Ono [4], Satoko Funaki [5], Naomi Tamura [5], Takahiro Kimoto [3], Maiko Jiko [6], Yuka Haruna [6], Akiko Sarashina [7], Masahiro Ishida [7], Kotaro Nishiyama [8], Masahiro Fushimi [9], Yukiko Kojima [9], Kazuhiro Yoneda [1], Misato Nakanishi [1], Soonih Kim [1], Takuya Fujita [10], Kiyohiko Sugano [11]

2002 ***2020***

The Only *Blinded* Comparison

Approx n=3000 !

Simulation output as submitted by contributors.

GastroPlus

Simcyp Simulator

Innovative Tools for Oral Biopharmaceutics

Extraction of API parameters and simulation output into a summary macro sheet.

OrBiTo API Data Files

Filtering and grouping based on parameters of interest.

Allowing statistical analysis to be carried out, visualised and automated.

Contents lists available at ScienceDirect

Computer Methods and Programs in Biomedicine

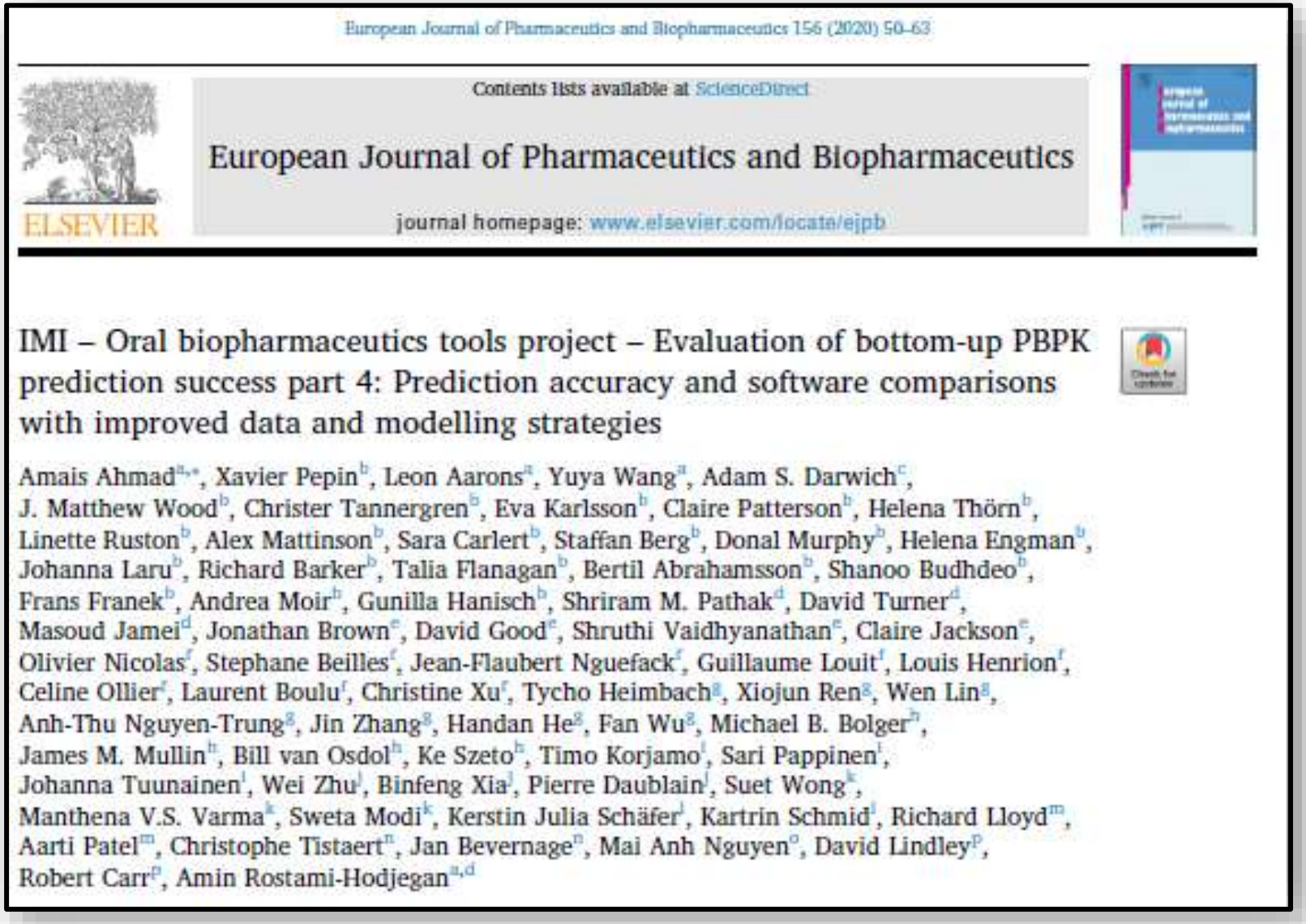
journal homepage: www.elsevier.com/locate/cmpb

Biopharmaceutics data management system for anonymised data sharing and curation: First application with orbito IMI project

Kristin Lacy-Jones[a,*], Philip Hayward[a], Steve Andrews[a], Ian Gledhill[a,1], Mark McAllister[b], Bertil Abrahamsson[c], Amin Rostami-Hodjegan[a,d], Xavier Pepin[e]

Average ***predictive performance did NOT clearly differ between software packages*** .

Some APIs showed a high level of variability in predictive performance across different software packages.
This variability could be related to several factors such as compound specific properties, the quality and availability of information, and errors in scaling from *in vitro* and preclinical *in vivo* data to human *in vivo* behaviour which will be explored further.



European Journal of Pharmaceutics and Biopharmaceutics 156 (2020) 50–63

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

IMI – Oral biopharmaceutics tools project – Evaluation of bottom-up PBPK prediction success part 4: Prediction accuracy and software comparisons with improved data and modelling strategies

Amais Ahmad[a,*], Xavier Pepin[b], Leon Aarons[a], Yuya Wang[a], Adam S. Darwich[c], J. Matthew Wood[b], Christer Tannergren[b], Eva Karlsson[b], Claire Patterson[b], Helena Thörn[b], Linette Ruston[b], Alex Mattinson[b], Sara Carlert[b], Staffan Berg[b], Donal Murphy[b], Helena Engman[b], Johanna Laru[b], Richard Barker[b], Talia Flanagan[b], Bertil Abrahamsson[b], Shanoo Budhdeo[b], Frans Franek[b], Andrea Moir[b], Gunilla Hanisch[b], Shriram M. Pathak[d], David Turner[d], Masoud Jamei[d], Jonathan Brown[e], David Good[e], Shruthi Vaidhyanathan[e], Claire Jackson[e], Olivier Nicolas[f], Stephane Beilles[f], Jean-Flaubert Nguefack[f], Guillaume Louit[f], Louis Henrion[f], Celine Ollier[f], Laurent Boulu[f], Christine Xu[f], Tycho Heimbach[g], Xiojun Ren[g], Wen Lin[g], Anh-Thu Nguyen-Trung[g], Jin Zhang[g], Handan He[g], Fan Wu[g], Michael B. Bolger[h], James M. Mullin[h], Bill van Osdol[h], Ke Szeto[h], Timo Korjamo[i], Sari Pappinen[i], Johanna Tuunainen[i], Wei Zhu[j], Binfeng Xia[j], Pierre Daublain[j], Suet Wong[k], Manthena V.S. Varma[k], Sweta Modi[k], Kerstin Julia Schäfer[l], Kartrin Schmid[l], Richard Lloyd[m], Aarti Patel[m], Christophe Tistaert[n], Jan Bevernage[n], Mai Anh Nguyen[o], David Lindley[p], Robert Carr[p], Amin Rostami-Hodjegan[a,d]

The Good, The Bad, and The Ugly
Model vs Data vs Modeller

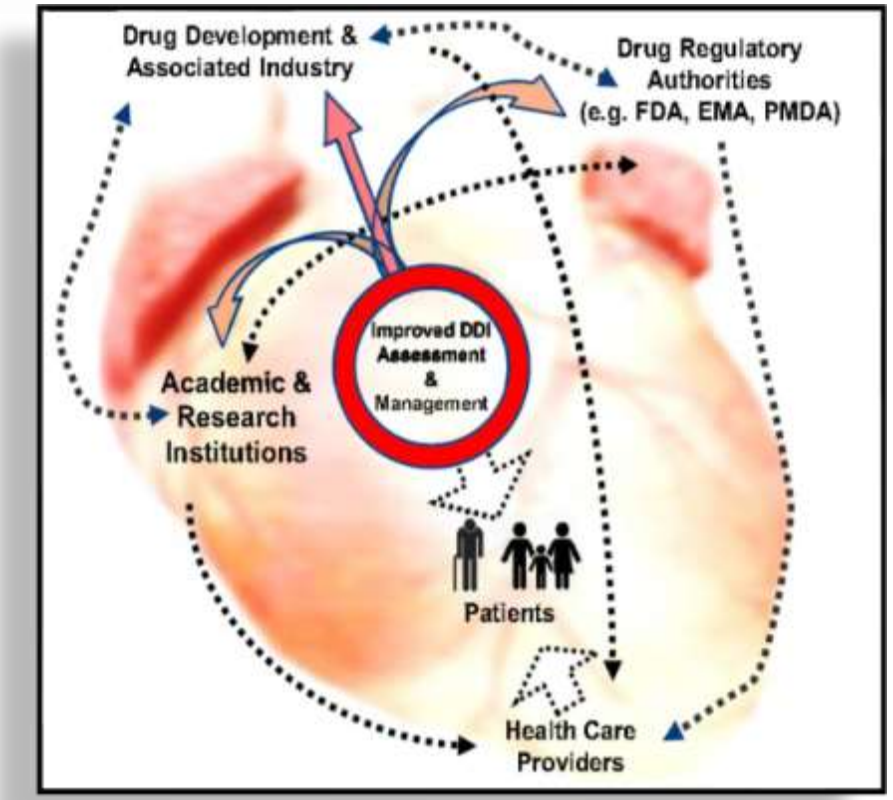
Come Dance With Me: Transformative Changes in the Science and Practice of Drug–Drug Interactions

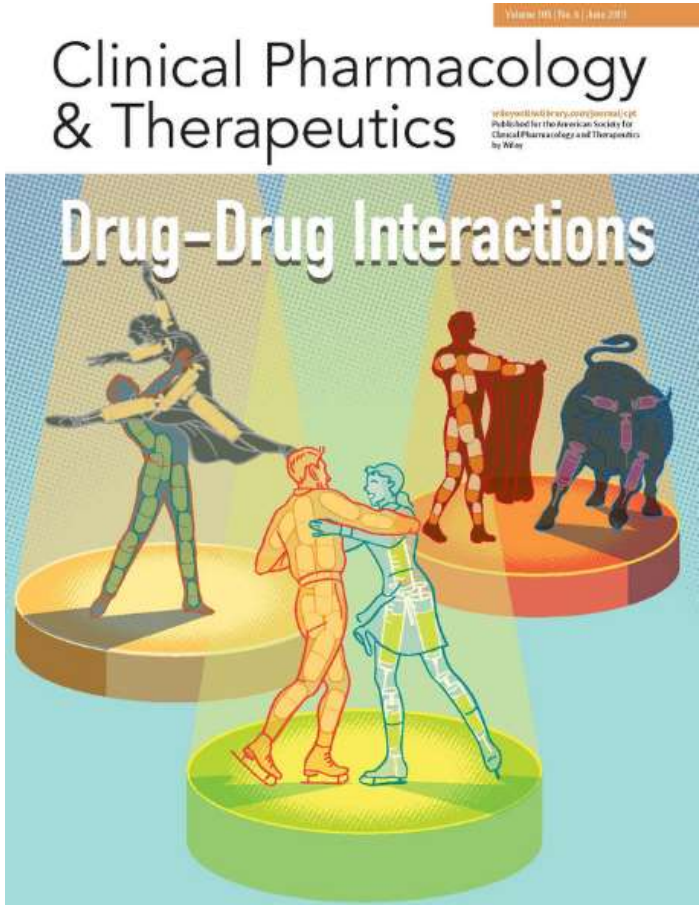
Karthik Venkatakrishnan[1,*] and Amin Rostami-Hodjegan[2,3]

EDITORIAL

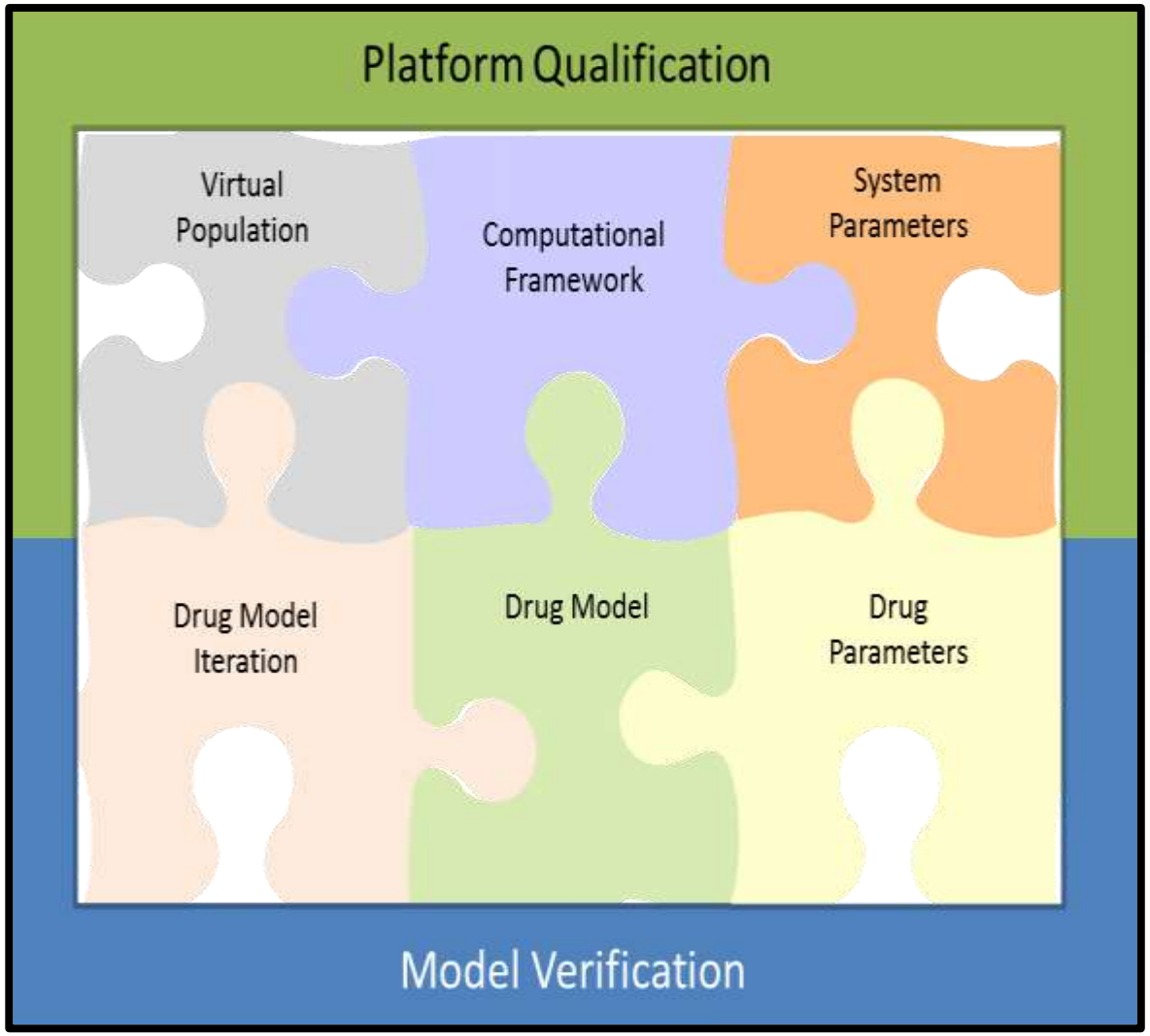
How M&S Became Ingrained in Drug Development for Assessing Drug-Drug Interactions:

- ***Collaboration*** **- Working together was at the heart of the matter**
- ***Integration*** **- Whole is more than sum of parts!**





A Consortium Approach:
Platform *vs* Model



Physiologically Based Pharmacokinetic Model Qualification and Reporting Procedures for Regulatory Submissions: A Consortium Perspective

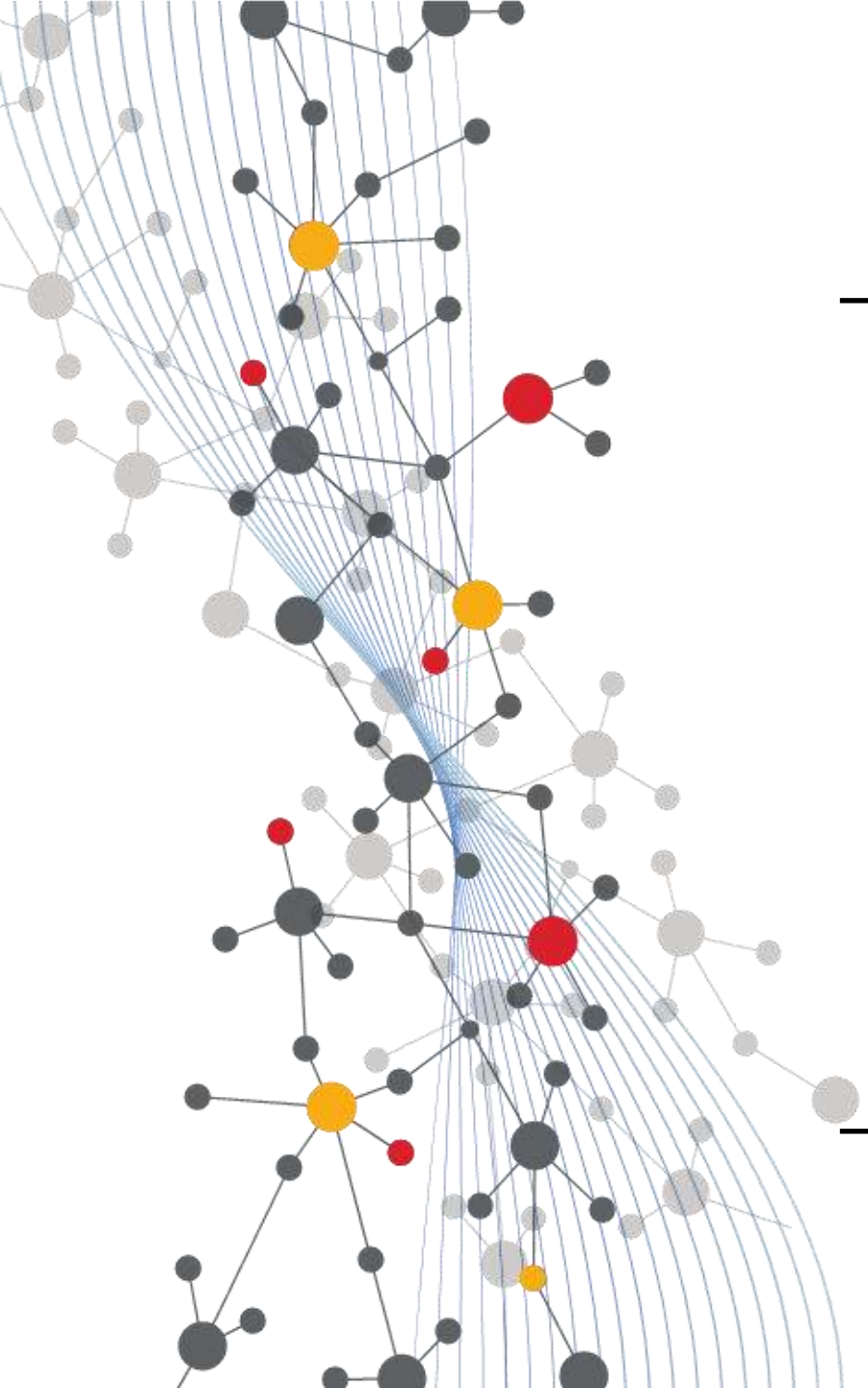
Mohamad Shebley[1], Punam Sandhu[2], Arian Emami Riedmaier[1], Masoud Jamei[3], Rangaraj Narayanan[4], Aarti Patel[5], Sheila Annie Peters[6], Venkatesh Pilla Reddy[7], Ming Zheng[8], Loeckie de Zwart[9], Maud Beneton[10], Francois Bouzom[11], Jun Chen[12], Yuan Chen[13], Yumi Cleary[14], Christiane Collins[15], Gemma L. Dickinson[16], Nassim Djebli[12], Heidi J. Einolf[17], Iain Gardner[3], Felix Huth[18], Faraz Kazmi[9], Feras Khalil[19], Jing Lin[20], Aleksandrs Odinecs[21], Chirag Patel[22], Haojing Rong[23], Edgar Schuck[24], Pradeep Sharma[7], Shu-Pei Wu[25], Yang Xu[26], Shinji Yamazaki[27], Kenta Yoshida[13] and Malcolm Rowland[28]

***CLINICAL PHARMACOLOGY & THERAPEUTICS*, 104 (1), JULY 2018**

General components of a **PBPK Analysis Package** for submission to regulatory health authorities.

Green Frame - The PBPK platform components that undergo qualification;

Blue Frame - The PBPK Component Files that undergo verification.



Topic for the Next 7 Minutes

The Elements of VERTICAL Growth:

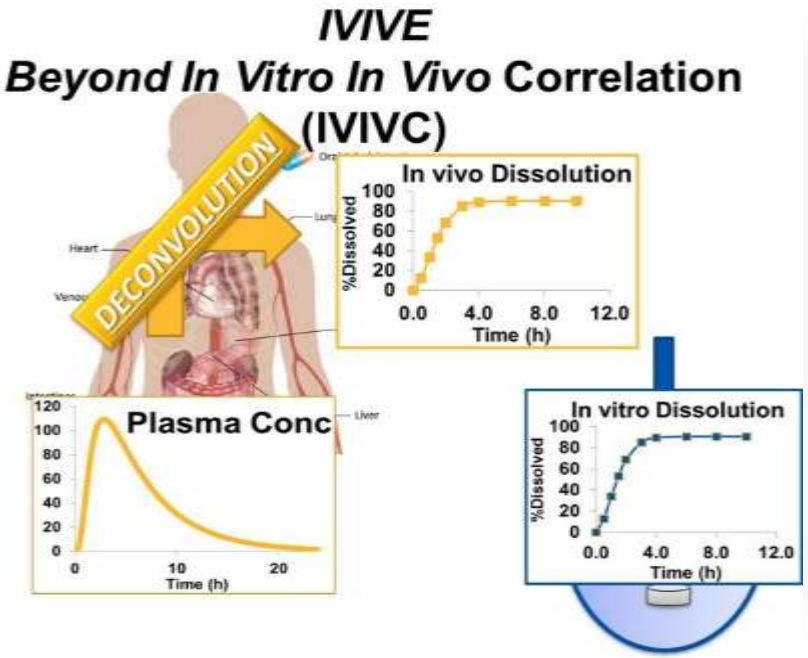
---

1. Identifying Unmet Needs

2. Thinking Outside the Box

3. Addressing Technical Issues

But, Do Not Forget That Someone Should Integrate All These of Pieces!



Public Workshop Summary Report on Fiscal Year 2021 Generic Drug Regulatory Science Initiatives: Data Analysis and Model-Based Bioequivalence

Framework & Vision

Jieon Lee[1], Yuqing Gong[1], Sid Bhoopathy[2], Charles E. DiLiberti[3], Andrew C. Hooker[4], Amin Rostami-Hodjegan[5,6], Stephan Schmidt[7], Sandra Suarez-Sharp[8], Viera Lukacova[8], Lanyan Fang[1] and Liang Zhao[1,*]

The AAPS Journal (2021) 23:31
DOI: 10.1208/s12248-021-00564-2

Records on Progress

Commentary

Biopharmaceutics Applications of Physiologically Based Pharmacokinetic Absorption Modeling and Simulation in Regulatory Submissions to the U.S. Food and Drug Administration for New Drugs

Fang Wu,[1,2,9] Heta Shah,[3] Min Li,[1] Peng Duan,[3] Ping Zhao,[4,5] Sandra Suarez,[3] Kimberly Raines,[1] Yang Zhao,[1,6] Meng Wang,[1,7] Ho-pi Lin,[1] John Duan,[3] Lawrence Yu,[8] and Paul Seo[1,9]

Biopharmaceutics & Drug Disposition

INVITED REVIEW

Scientific Considerations to Move Towards Biowaiver for BCS Class III Drugs:How Modeling and Simulation Can Help?

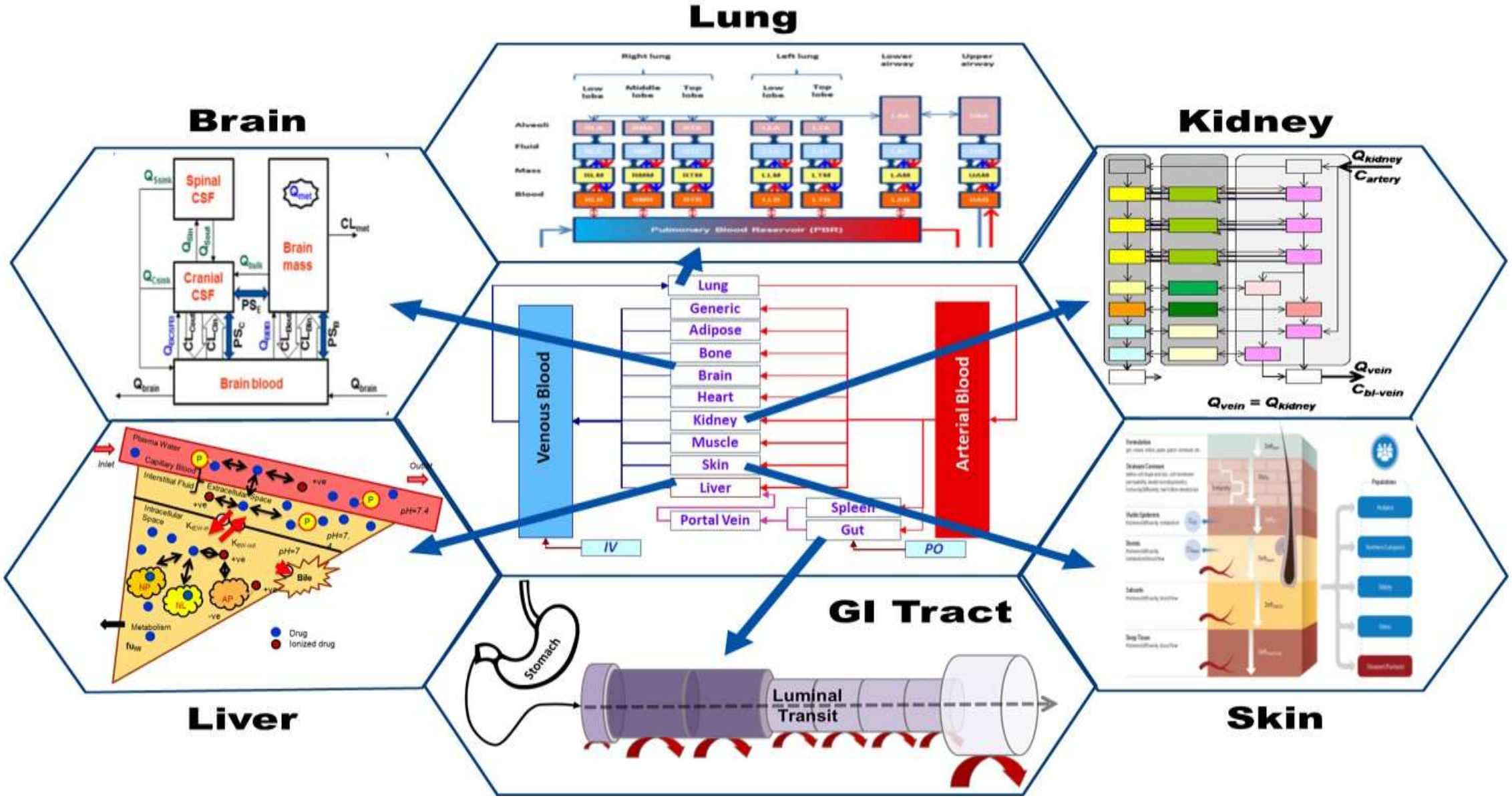
Fang Wu, Rodrigo Cristofoletti, Liang Zhao ✉, Amin Rostami-Hodjegan

First published: 23 March 2021 | https://doi.org/10.1002/bdd.2274

Vertical Dive
(Example from Specific Areas)

More Mechanistic Sub-Models of Organs

Modern PBPK Models Can Contain Many Routes of Administration and Specifications for Each Organ:



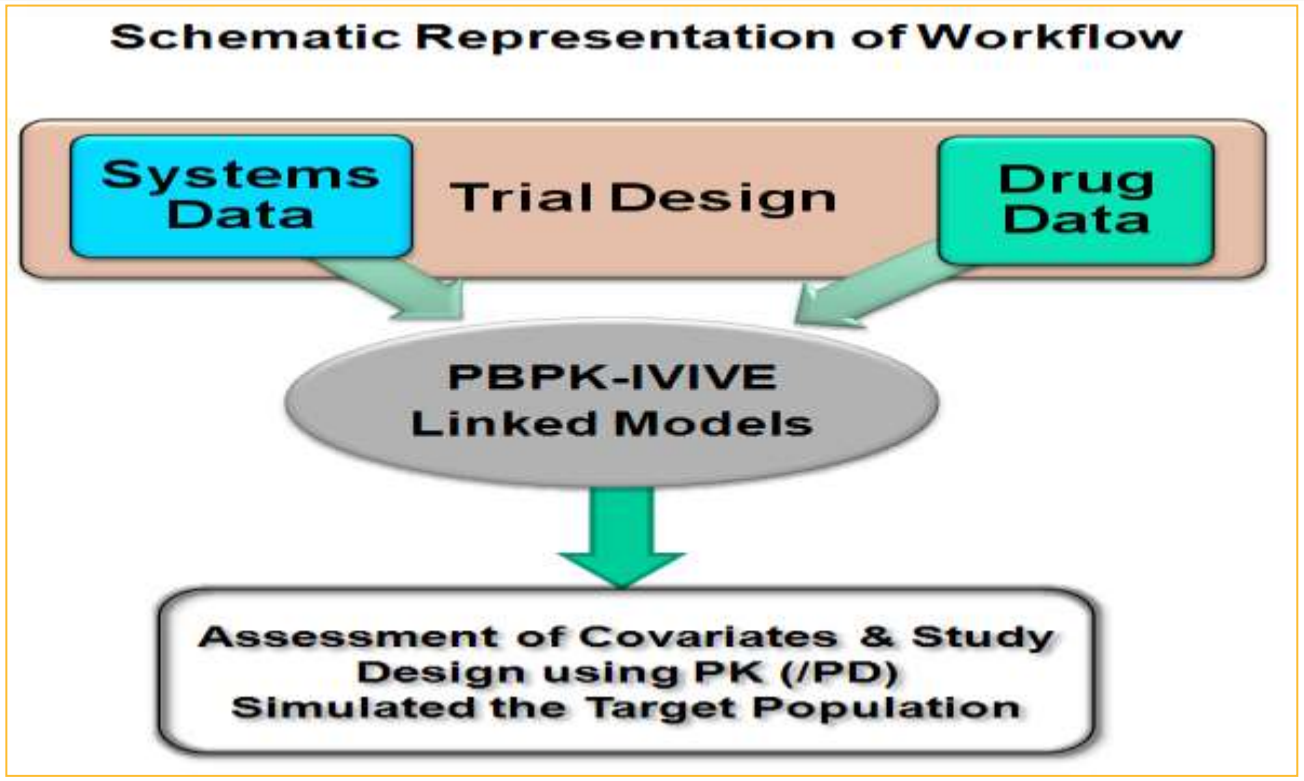
PBPK/IVIVE: Breaking Down the Information to Enable Rebuilding Virtual Clinical Studies

STATE OF THE ART

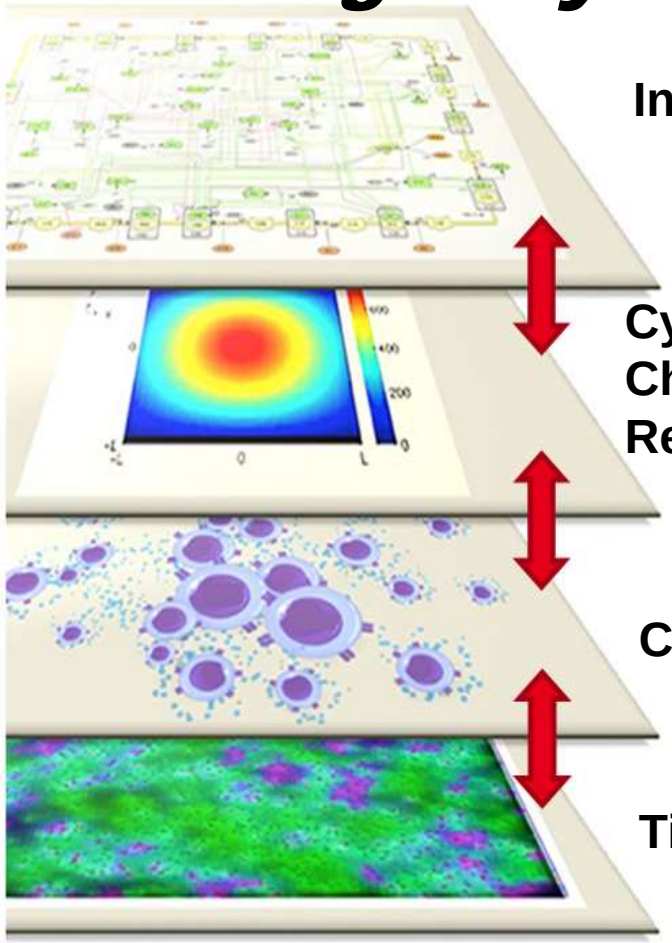
nature publishing group

Physiologically Based Pharmacokinetics Joined With *In Vitro–In Vivo* Extrapolation of ADME: A Marriage Under the Arch of Systems Pharmacology

A Rostami-Hodjegan[1,2]

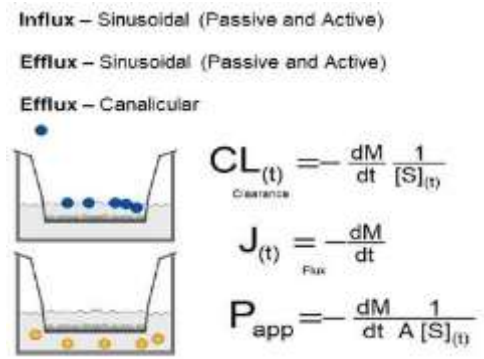


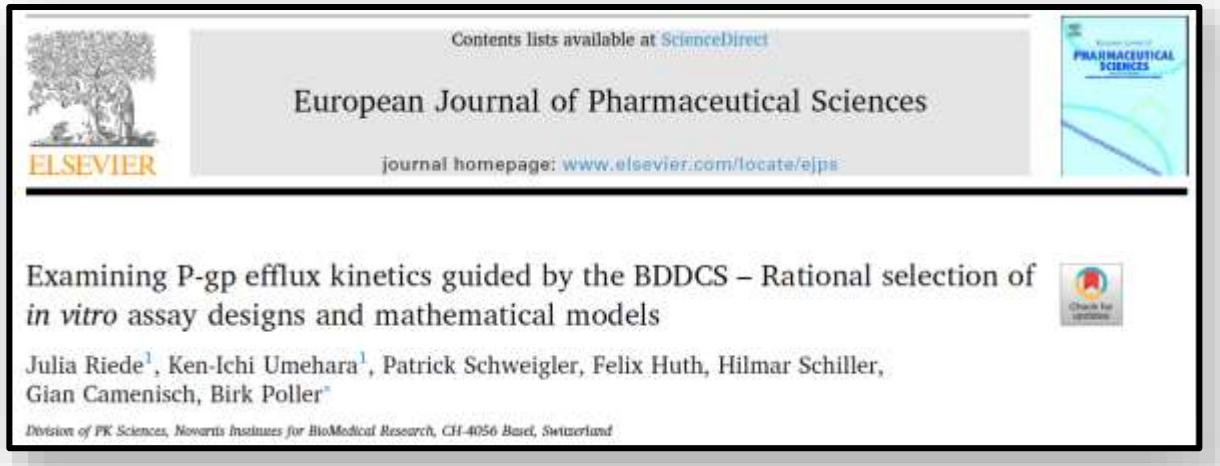
In Vitro Tools *to Assess the Interplay of Drug & System*



Ability to Analyse Data and Obtain *'Intrinsic Parameters'* *(Dedicated In Vitro Data Analysis Tool are Required)*

Say NO to Single Point Semi-Quantitative Measures




Contents lists available at ScienceDirect

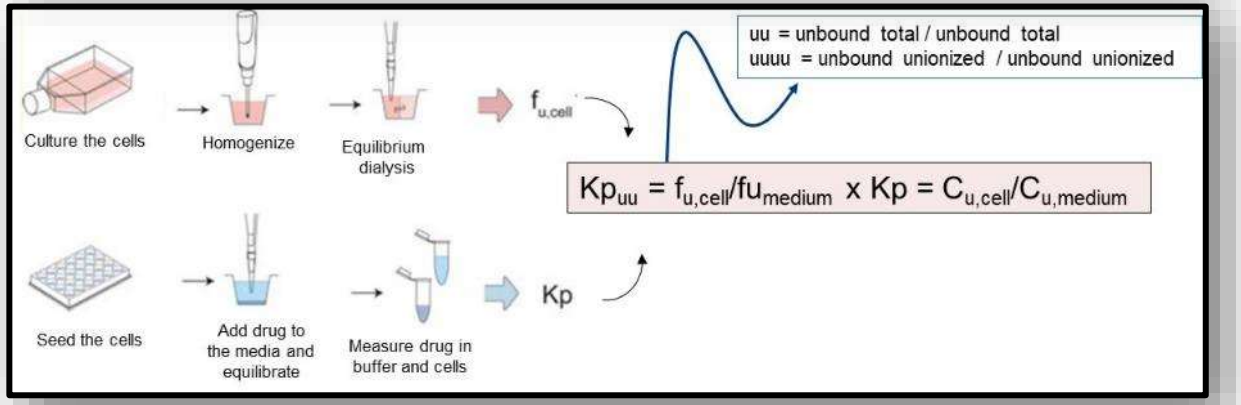
European Journal of Pharmaceutical Sciences

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

Examining P-gp efflux kinetics guided by the BDDCS – Rational selection of *in vitro* assay designs and mathematical models

Julia Riede[1], Ken-Ichi Umehara[1], Patrick Schweigler, Felix Huth, Hilmar Schiller, Gian Camenisch, Birk Poller*

Division of PK Sciences, Novartis Institutes for BioMedical Research, CH-4056 Basel, Switzerland

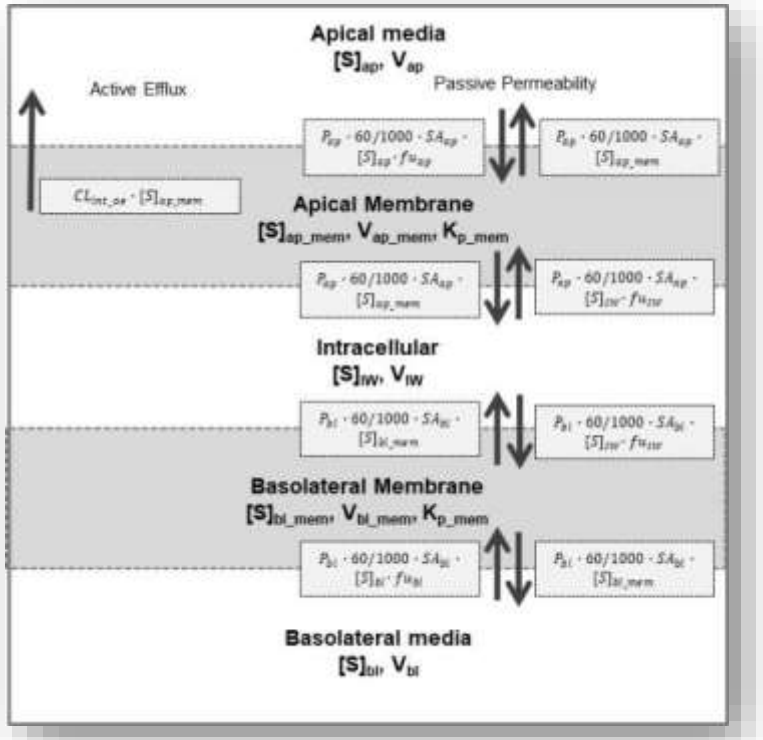


Wave Goodbye to

A to B / B to A Ratio!

Green
=
Drug
Parameters

Blue
=
System
Parameters



Understanding the Interplay of Systems with the Excipients & Formulation in addition to API (Drug Itself)

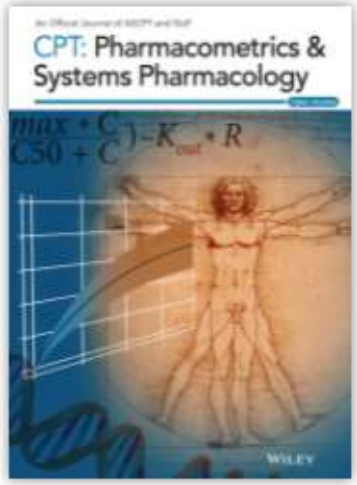
CPT: Pharmacometrics & Systems Pharmacology

ARTICLE | Open Access

Excipient Knowledgebase: Development Of A Comprehensive Tool For Understanding The Disposition And Interaction Potential Of Common Excipients

Savannah J. McFeely, Jingjing Yu, Yan Wang, Cheryl Wu, Isabelle Ragueneau-Majlessi

First published: 08 June 2021 | https://doi.org/10.1002/psp4.12668



Accepted Articles

Accepted, unedited articles published online and citable. The final edited and typeset version of record will appear in the future.

Robust Mechanistic M&S Requires Systems Data!

Protein Abundance & Inter-Correlations in Health & Disease

Quantitative Proteomics of Clinically Relevant Drug-Metabolizing Enzymes and Drug Transporters and Their Intercorrelations in the Human Small Intestine

Narciso Couto, Zubida M. Al-Majdoub, Stephanie Gibson, Pamela J. Davies, Brahim Achour, Matthew D. Harwood, Gordon Carlson, Jill Barber, Amin Rostami-Hodjegan, and Geoffrey Warhurst

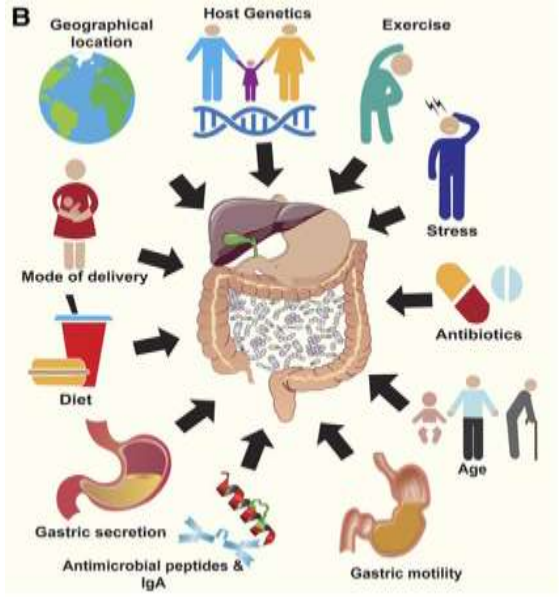
Drug Metabolism Disposition 2020

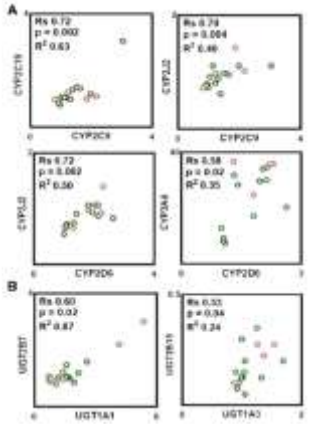
ARTICLE

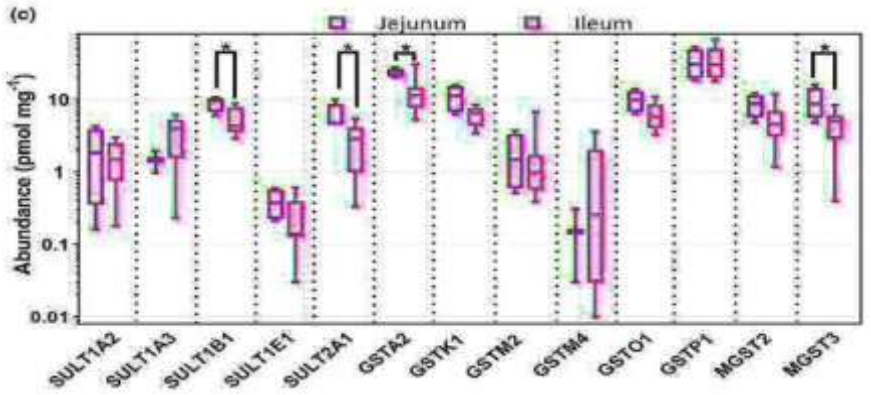
Quantification of Proteins Involved in Intestinal Epithelial Handling of Xenobiotics

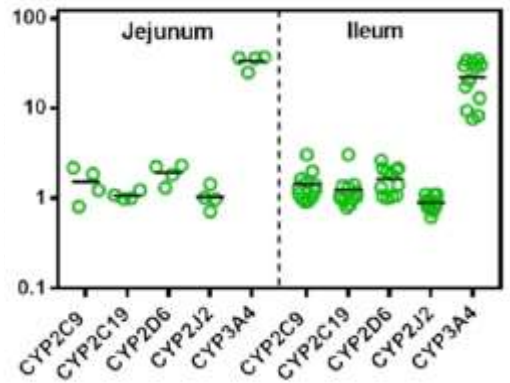
Zubida M. Al-Majdoub[1,*], Narciso Couto[1], Brahim Achour[1], Matthew D. Harwood[2], Gordon Carlson[3], Geoffrey Warhurst[3], Jill Barber[1] and Amin Rostami-Hodjegan[1,2]

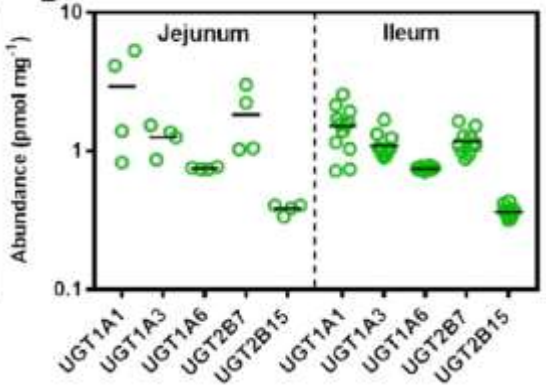
Clin Pharmacol Ther 2020











Yes, Robust Mechanistic M&S Requires Systems Data!

Protein Abundance & Inter-Correlations in Health & Disease

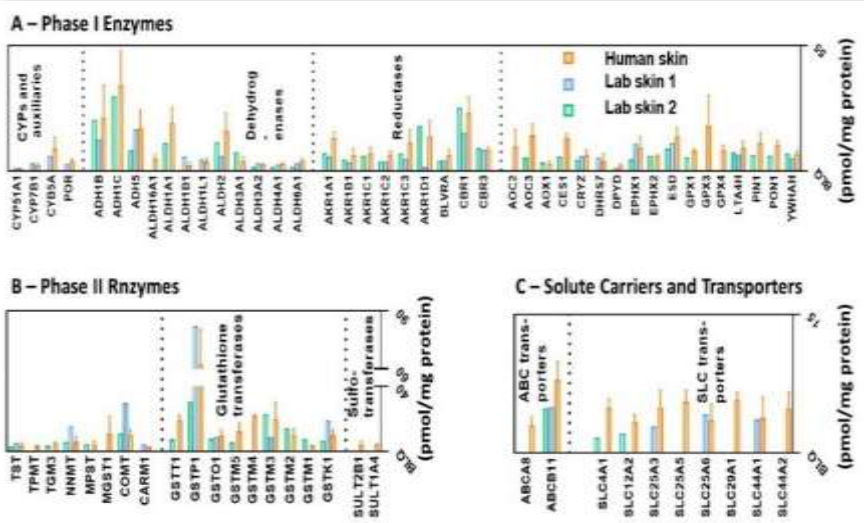
BUT .....

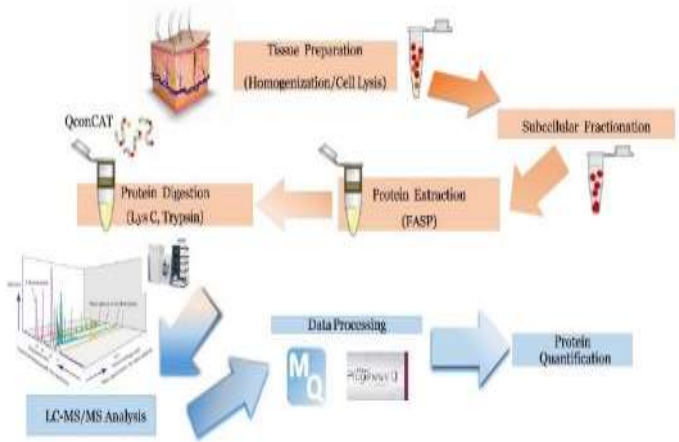
Such Details Are ***SPARSE*** for Non-Oral Routes of Administration

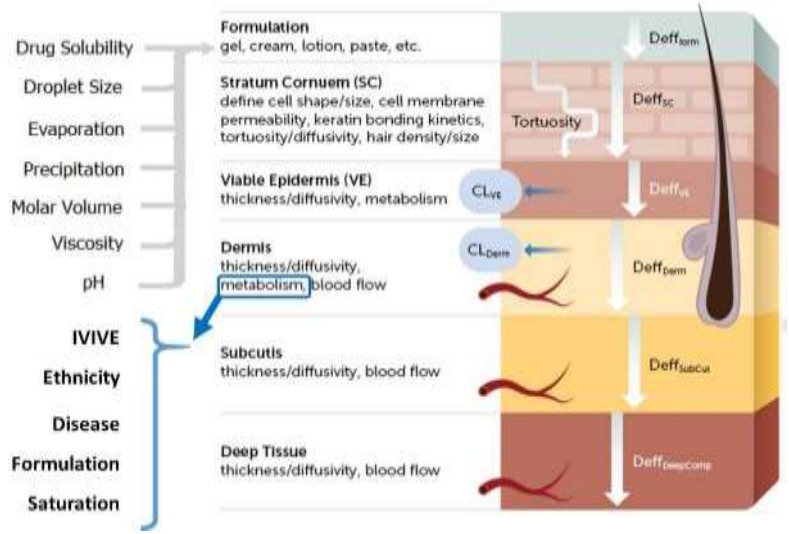
1521-009X/49/1/39–52$35.00
DRUG METABOLISM AND DISPOSITION
https://doi.org/10.1124/dmd.120.000168
Drug Metab Dispos 49:39–52, January 2021

Label-Free Quantitative Proteomics and Substrate-Based Mass Spectrometry Imaging of Xenobiotic Metabolizing Enzymes in Ex Vivo Human Skin and a Human Living Skin Equivalent Model

Narciso Couto, Jillian R.A. Newton, Cristina Russo, Esther Karunakaran, Brahim Achour, Zubida M. Al-Majdoub, James Sidaway, Amin Rostami-Hodjegan, Malcolm R. Clench, and Jill Barber







On A More Positive Note:

The Vision by the Regulatory Agency, the Encouragement from Case Examples, and a Similar Path to Novel Ways for Establishing BE Are in Place:

Welcome to the V-BE World!

FY 2020 Generic Drug Regulatory Science Initiatives Public Workshop, May 4th 2020

Physiologically-based pharmacokinetic modeling to support bioequivalence and approval of generic products: A case for diclofenac sodium topical gel, 1%

Eleftheria Tsakalozou | Andrew Babiskin | Liang Zhao

***CPT Pharmacometrics Syst. Pharmacol.* 2021**

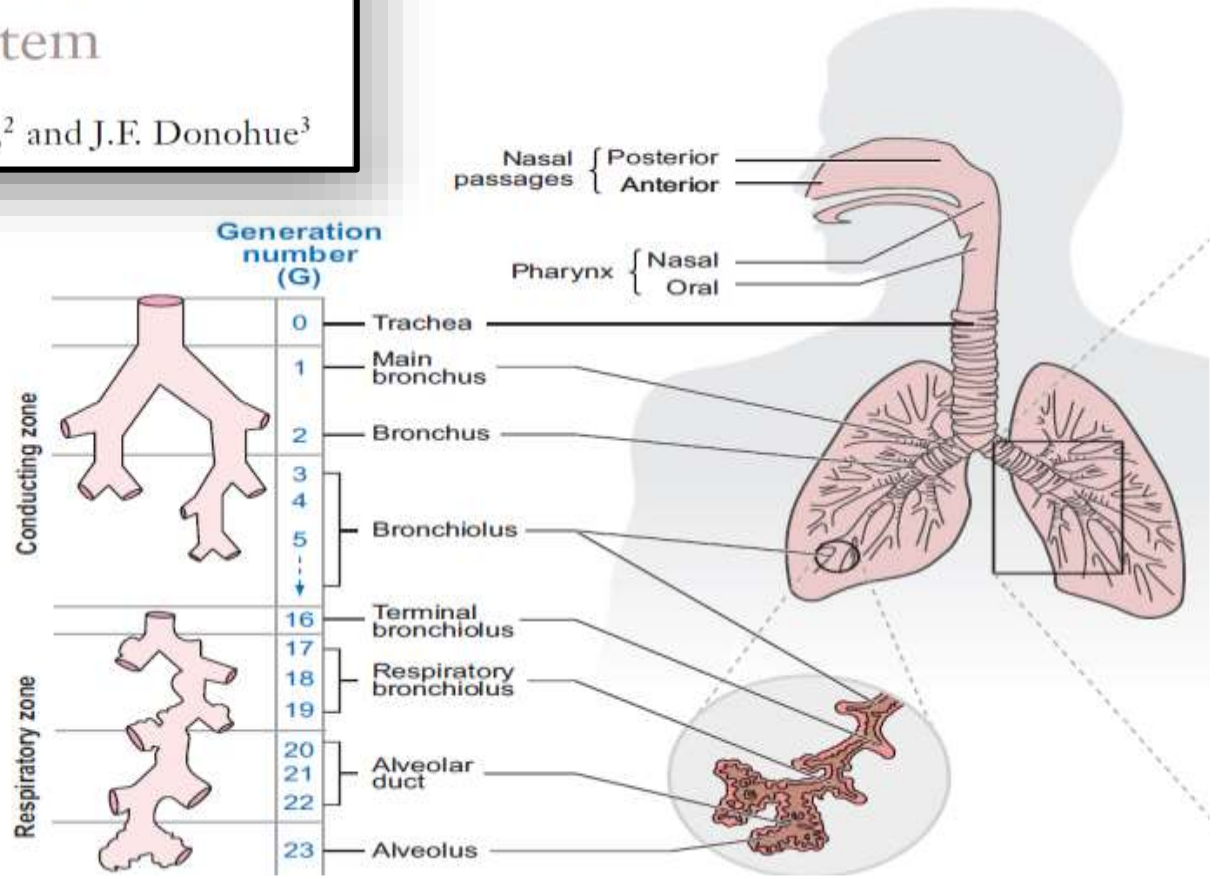
What About Other Routes of Administration:

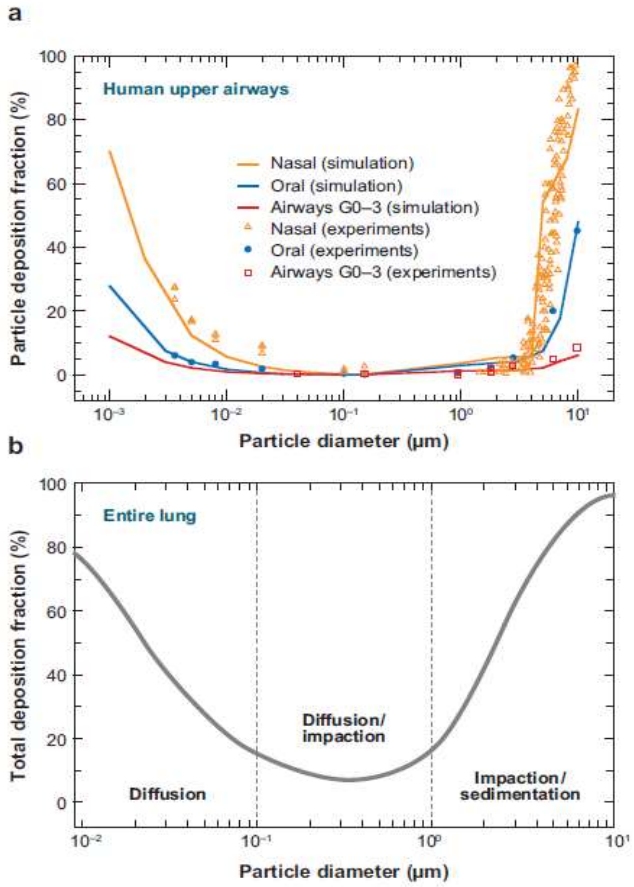
NOT Short of Models: Well Established But ….

Targeted Drug-Aerosol Delivery in the Human Respiratory System

C. Kleinstreuer,[1] Z. Zhang,[2] and J.F. Donohue[3]

Annul Rev. Biomed. Eng. (2008) 10:195–220

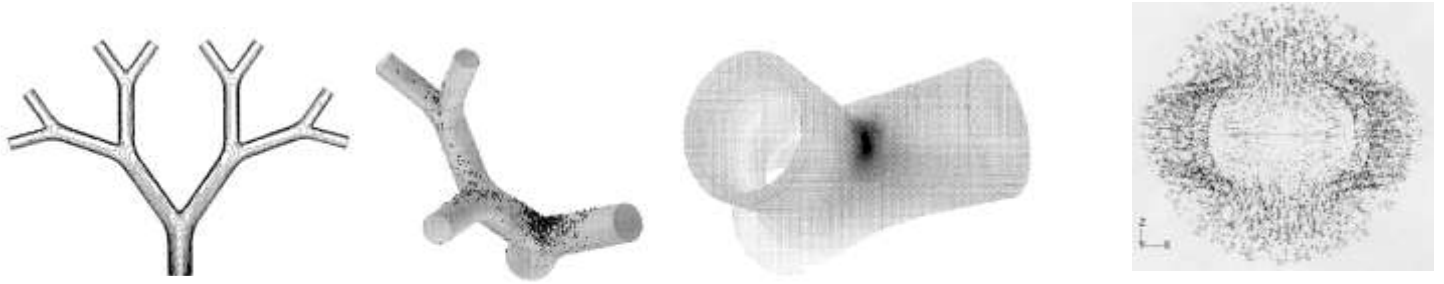




..... Short of Systems Data (in Health & Disease)/ Integration/Verification/Consensus/User-Friendly Tool

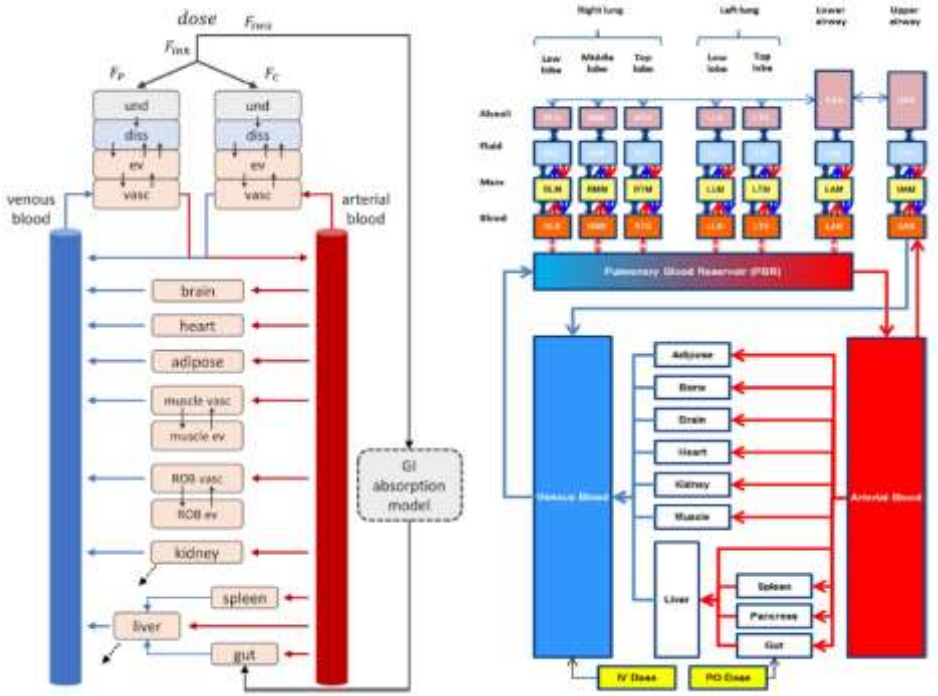
Computational Fluid Dynamics (CFD) Models

There are many CFD models for pulmonary drug deposition of inhaled particles. However, there are not sets of agreed physiological parameters to go with such models.



The FLUENT CFD Package (2003) Fluent Europe Co., Ltd Sheffield, UK

Bala´sha´zy et al. *Radiation Protection Dosimetry* 105 (1–4). 129–132 (2003)

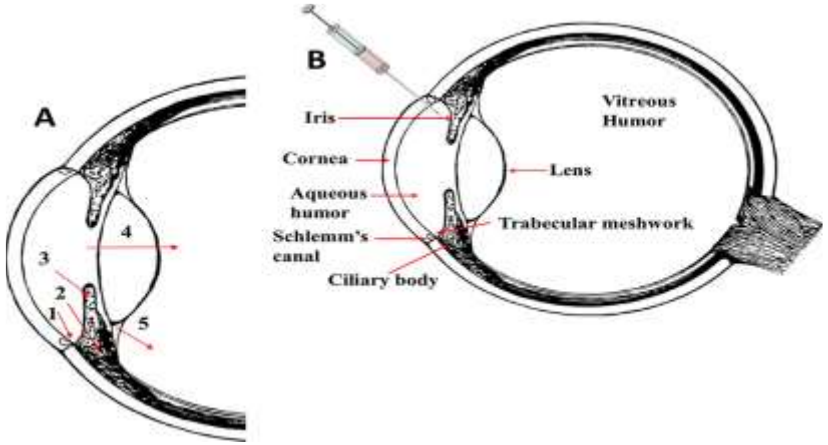


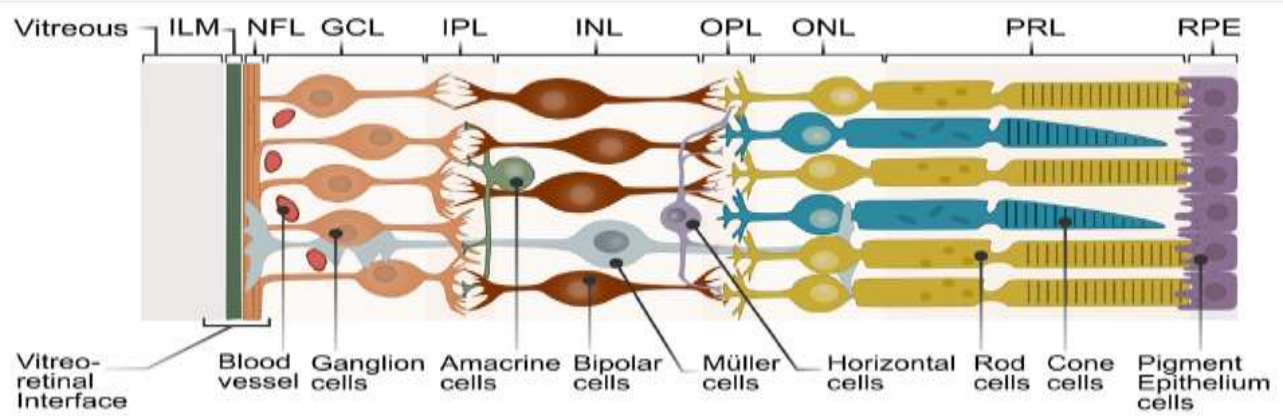
Integrating Pulmonary Drug Deposition with Local Drug Disposition

CFD Should Joins Forces with PBPK

PBPK models for pulmonary administration (e.g. Gaohua et al, 2015) consider the permeability-limited aspects where formulation effects can be accounted for. They also consider inter-correlations of system parameters to simulate true population variability better. However, biological values of human transporters and enzymes in the lung tissue are missing and CFD models are rarely integrated with PBPK models.

…. the Same Story: Short of Systems Data (in Health & Disease)/Integration/Verification/ Consensus/Options for User-Friendly Tool!

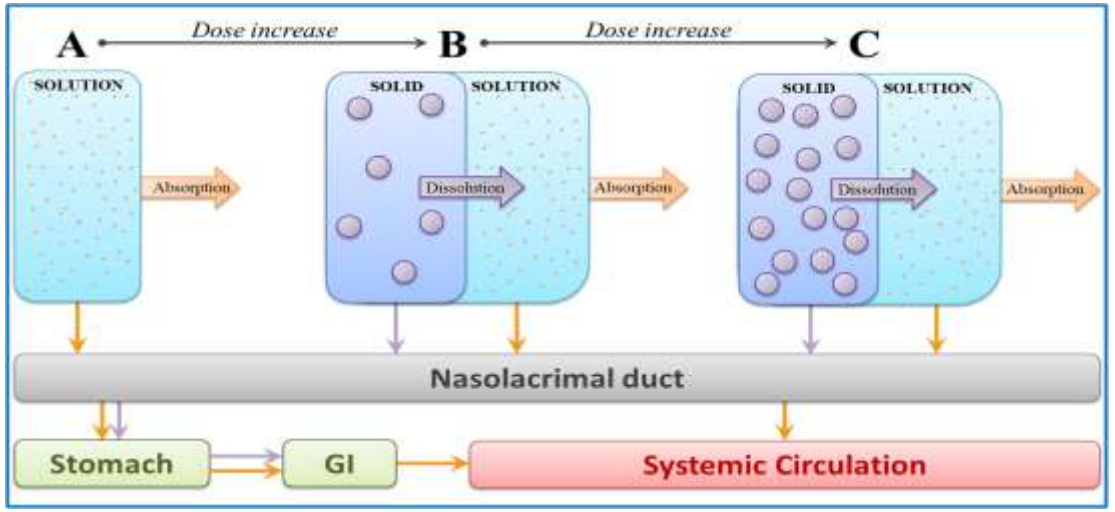




Ocular Drug Disposition

Intracameral injection involves multi-step clearance (Fayyaz et al, 2020), with vitreous and vitreoretinal barriers (Tavakoli et al 2020), all poorly understood.

Models for topical administration consider many non-linearity issues related to dose and rate of absorption (Le Merdy *et al,* 2020b). However, these models do not consider any local metabolism or transporter-mediated efflux or uptake and formulatiom impact on these.



Biopharmaceutics Work Bench: Last Stop for VBE

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

General Commentary

Past, Present, and Future of Bioequivalence: Improving Assessment and Extrapolation of Therapeutic Equivalence for Oral Drug Products

Rodrigo Cristofoletti [1,2], Malcolm Rowland [3], Lawrence J. Lesko [4], Henning Blume [5], Amin Rostami-Hodjegan [3,6], Jennifer B. Dressman [2,*]

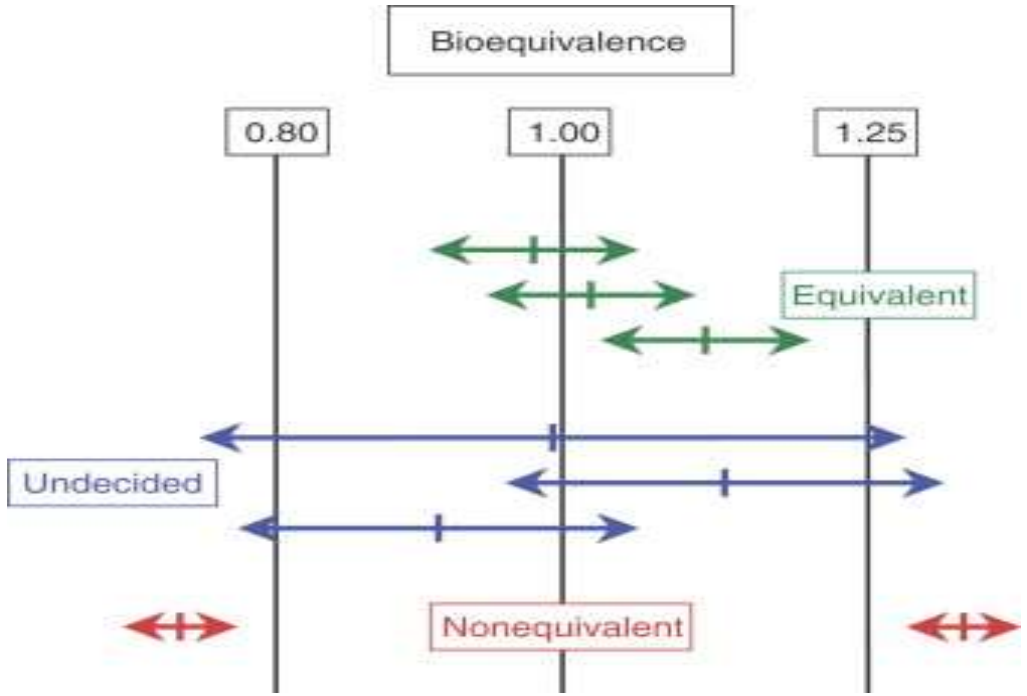
J Pharm Sci 2019

Propagation of Intra-Subject Variability in Attributes of Gi-Tract to Bioavailability of Drugs and Implications for the Design of Bioequivalence Studies

Margareta Bego, MSc Thesis, MIDD Course, University of Manchester
Agency for Medicinal Products and Medical Devices, Zagreb, Croatia

June 2021

Virtual Bioequivalence (VBE) & Inter-Occasion/Within-Subject (IOV/WSV)



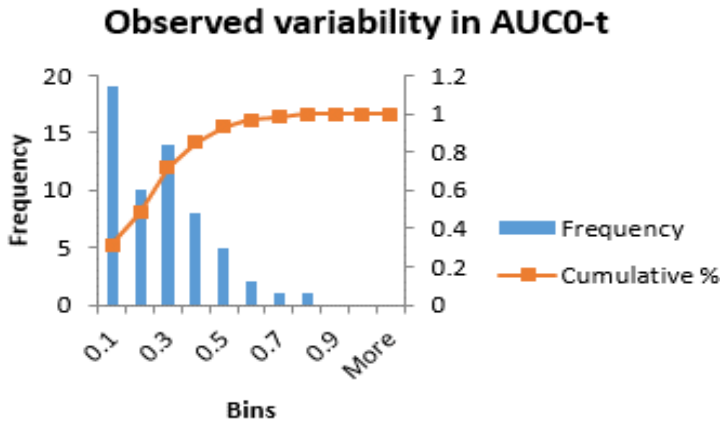
Finding IOV/WSV Combinations of Physiological Parameters which are INCOMPATIBLE with Observed IOV/WSV of PK

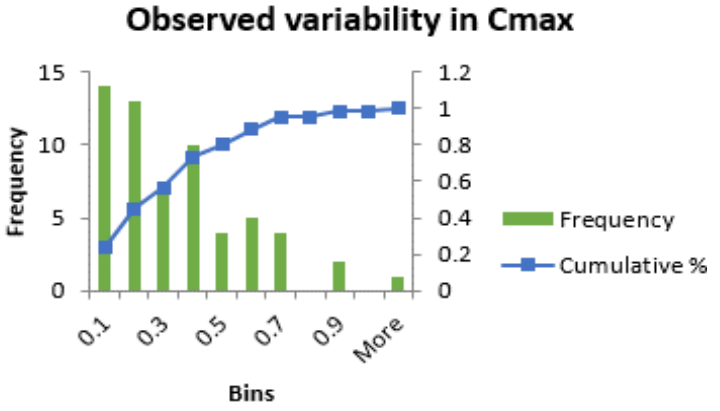
Parameters investigated/ Sensitive PK parameters	Cmax	Tmax	AUC
Initial volume of stomach fluid	Yes ↑	Yes ↓	Yes ↑
Stomach pH	No	No	No
Duodenum pH	Yes ↑	Yes ↓	Yes ↑
Jejunum I pH	Yes ↑	Yes ↓	Yes ↑
Jejunum II pH	Yes ↑	Yes ↓	Yes ↑
Stomach MRT	Yes ↓	Yes ↑	Yes ↓
Small intestine MRT	Yes ↑	Yes ↑	Yes ↑
Colon MRT*	No	No	Yes ↑
IMMC Cycle time	No	No	No
Duodenum bile salts level	No	No	No
Jejunum I bile salts level	Yes ↑	Yes ↓	Yes ↑
Jejunum II bile salts level	Yes ↑	Yes ↓	Yes ↑
Duodenum bicarbonate level	No	No	No
Jejunum I bicarbonate level	No	No	No
Jejunum II bicarbonate level	No	No	No

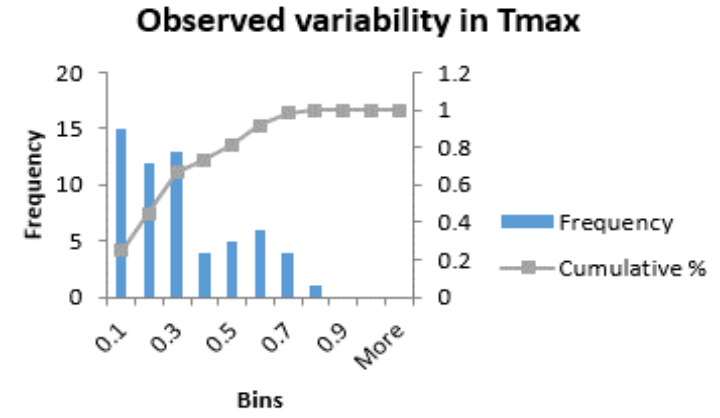
- *slight changes in Cmax and Tmax, not deemed relevant*
- *Arrows show direction of change with an increase of the GI parameter value*

	Observed vs Predicted Distributions (AUC, Cmax and Tmax) (Kolmogorov-Smirnov Test)					
COMB	D statistic AUC	Similarity (Y/N)	D statistic Cmax	Similar(ity Y/N)	D statistic Tmax	Similarity (Y/N)
(default)	0.350	No	0.417	No	0.200	Yes
24-1	0.200	Yes	0.217	Yes	0.150	Yes
24-2	0.167	Yes	0.150	Yes	0.217	Yes
24-3	0.367	No	0.367	No	0.217	Yes
24-4	0.133	Yes	0.200	Yes	0.133	Yes
24-5	0.267	No	0.317	No	0.183	Yes
24-6	0.183	Yes	0.250	No	0.167	Yes
24-7	0.217	Yes	0.167	Yes	0.133	Yes
24-8	0.167	Yes	0.167	Yes	0.183	Yes
24-9	0.233	Yes	0.317	No	0.200	Yes
24-10	0.217	Yes	0.233	Yes	0.183	Yes
24-11	0.200	Yes	0.183	Yes	0.133	Yes
24-12	0.300	No	0.250	No	0.133	Yes
24-13	0.317	No	0.333	No	0.217	Yes
24-14	0.133	Yes	0.167	Yes	0.217	Yes

Two-sample KS:
p-value > 0.05 = null hypothesis cannot be rejected (two samples follow the same distribution);
p-value < 0.05 = null hypothesis should be rejected (the distributions of two samples are different);
Hence, highlighted cells – IOV Model Not Supported



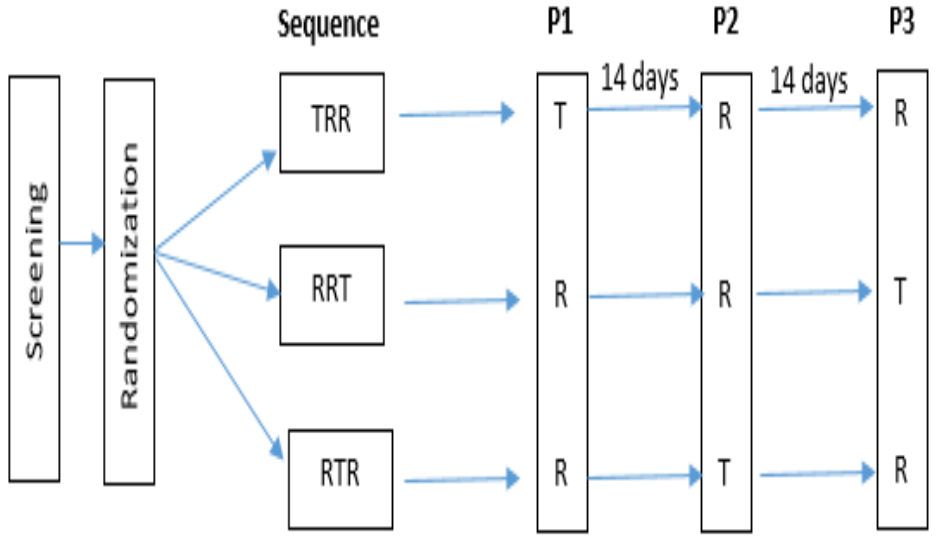


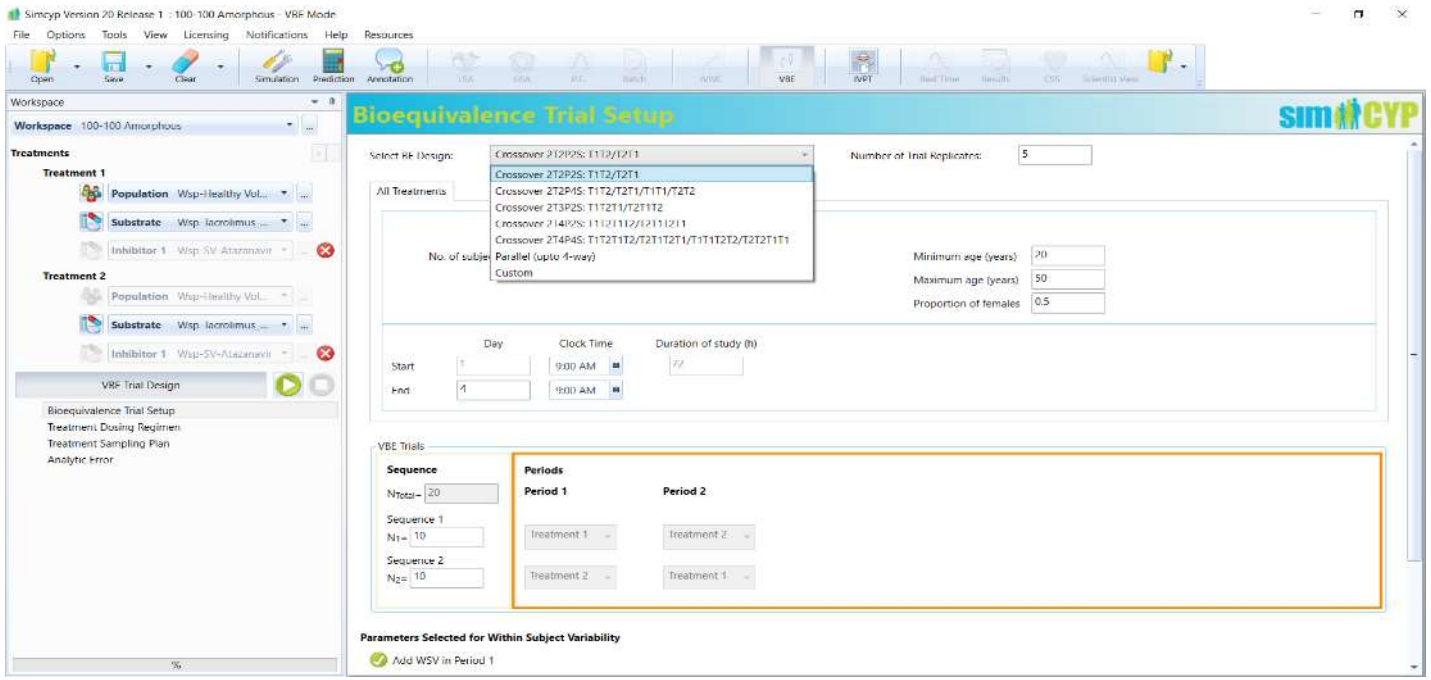


The Gold Mine of RTR Studies

(Reference-Test-Reference Cross-Over BE)

FDA DATABASE OF VARIOUS DRUGS
and
VARIOUS FORMULATIONS
to
Gaining Insight into
DRUG- & FORMULATION-INDEPNDENT
IOV/WSV of the Physiology and Biology!





These Can be Incorporated
to
ANY User-Friendly
M&S Tools
Specifically Built
for

VBE

(Instead of Arbitrary IOV/WSV)

Summary Points (in 1 Minute)

1. **CONSENSUS** on Existing Selection of Models for Scale Up and Routine Use
2. **INTEGRATION** of More Systems Data to Platforms from 'Open Data Initiatives'
3. **MODELLING** *In Vitro* Experimental Data & Taking the Outputs as Input for Quantitative VBE Models
4. **INCENTIVES** by Publicising Accepted Robust/Verified Models to Increase Wider Use and Show Reduced Risk
5. **REVERSE TRANSLATION** of Historic Clinical Data for Obtaining IOV/WSV of Physiology & Using Bayesian Fitting as Part of Common Mechanistic M&S VBE Tools
6. **ALLOW** Occasional Off-the-Main Road M&S by F1 Drivers Exploring Knowledge Gaps & New Limits
7. **DEFINE** Guides (SOP's) & Licences for Established M&S Tools by Drivers Who Are on the Main Road

Thanks for Listening

Questions?