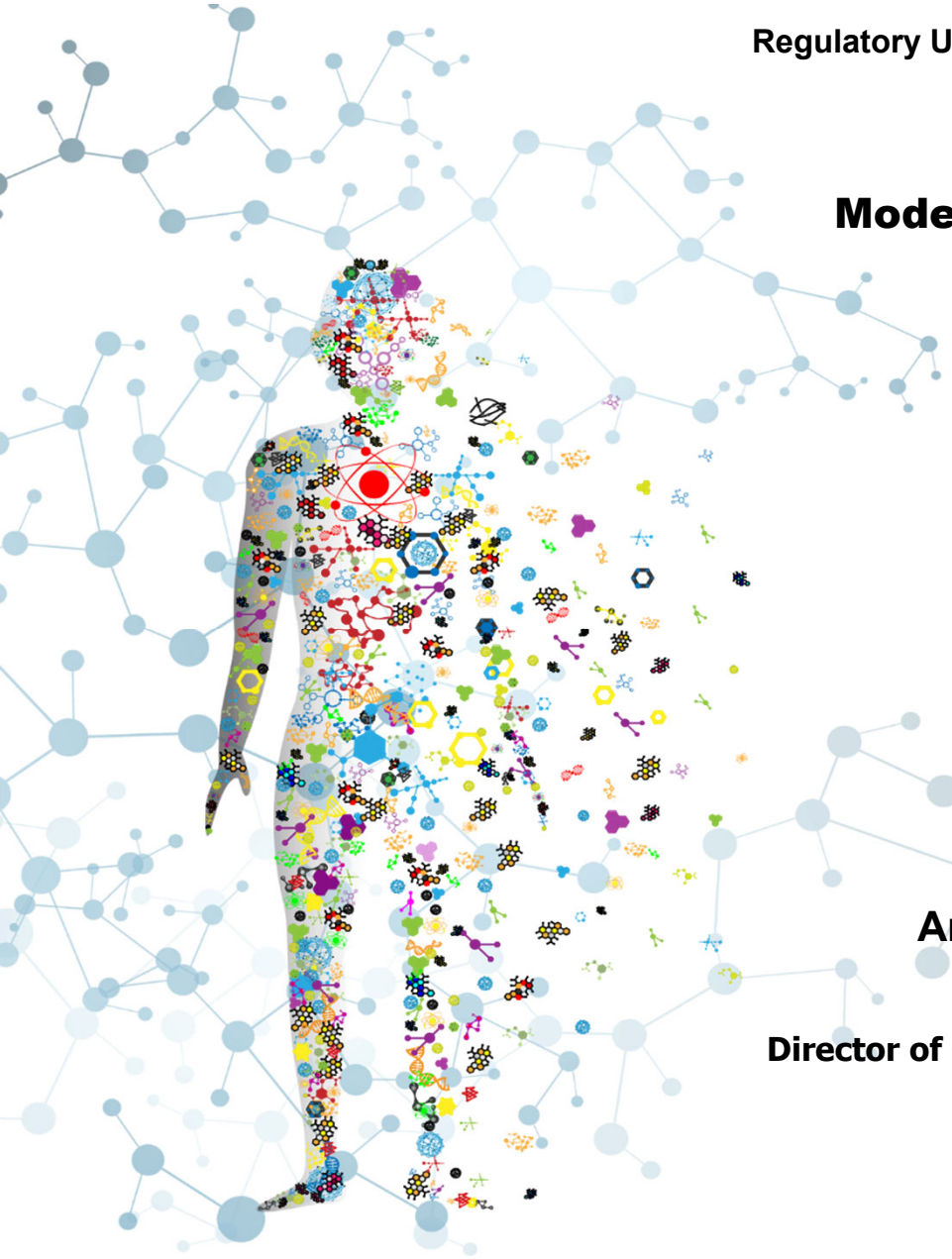


Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches
Virtual Public Workshop - September 30th and October 1st 2021

Symposium III/Session 4:
Model Acceptance and Model Sharing for Regulatory Use

Model Master File (MMF)

Non-Regulatory Perspective:

What Can Be a MMF and How to Share It?

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

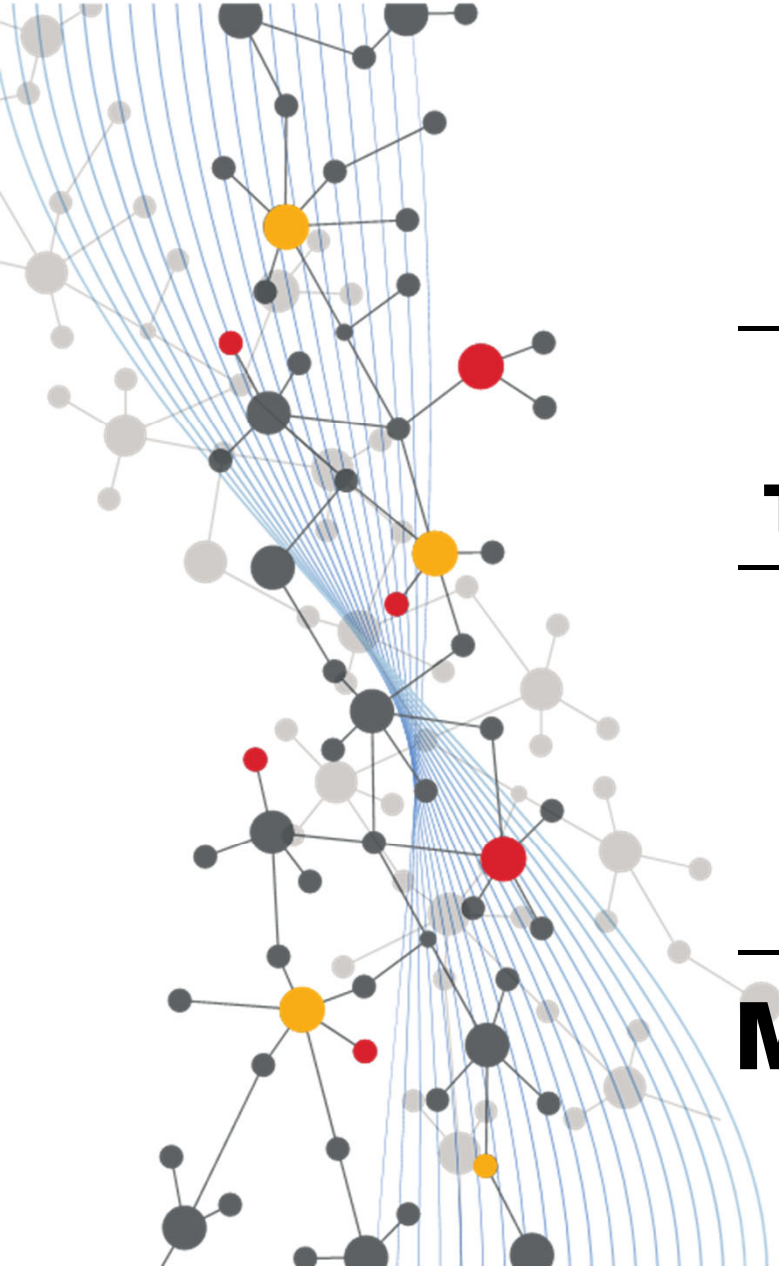
Declaration of Conflict of Interest

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 and Servier) 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 pharmacology and 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 12 Minutes

DATA

Drug/Formulation *vs* Systems

MODELS

Top-Down vs Bottom-Up vs Middle-Out

SHARING

"What to Share?"

"What the Benefits Are?"

"Who Are the Beneficiaries?

MASTER FILE → PLATFORM

"Is There Evidence of Impact?"

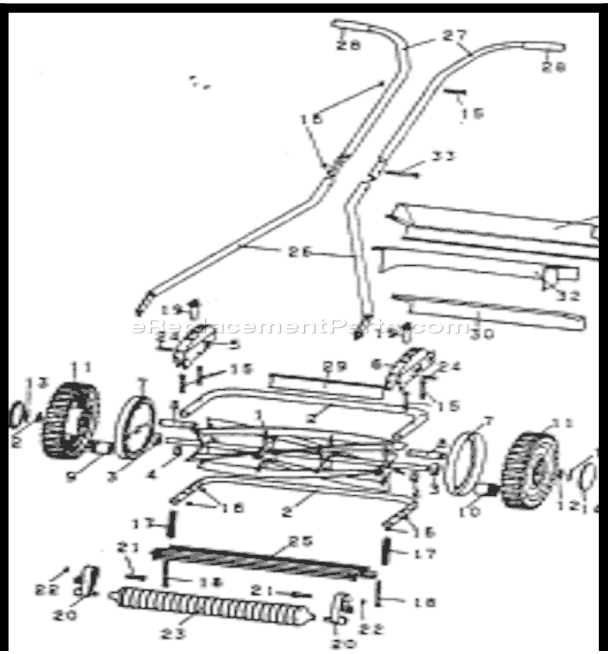
Borrowing Your Neighbour's Lawn Mower?

Starting from Scratch Is NOT AN IDEAL OPTION!

Source Data
(Pile of Components)

Wheel Gaurd LH		238	Caster LH		13	Tie Bar		
Wheel Gaurd RH		238	Caster RH		13	Wheel Arch Clamp LH		9
Frame Front LH		205	Main Cover Rear		88	Wheel Arch Clamp RH		9
Frame Front RH		205	Control Box		40	Motor Bracket LH		31
Frame LH Rear		299	Main Cover LH		143	Motor Bracket RH		31
Frame RH Rear		299	Main Cover RH		143	Wheel Arch Support LH		31
Back Facia			Blade Disc		110	Wheel Arch Support RH		31
Center Facia		105	Mower Motor Clamp Frnt		27	Fan Blade Bracket		21
Facia LH		112	Rear Wheel		596	Fan Cover Motor		5
Facia RH		112	Rear Wheel		596	Rear Air Cover		5
Frame Clamp			Mower Motor Clamp Rear		27	Total Weight 3.78KG		

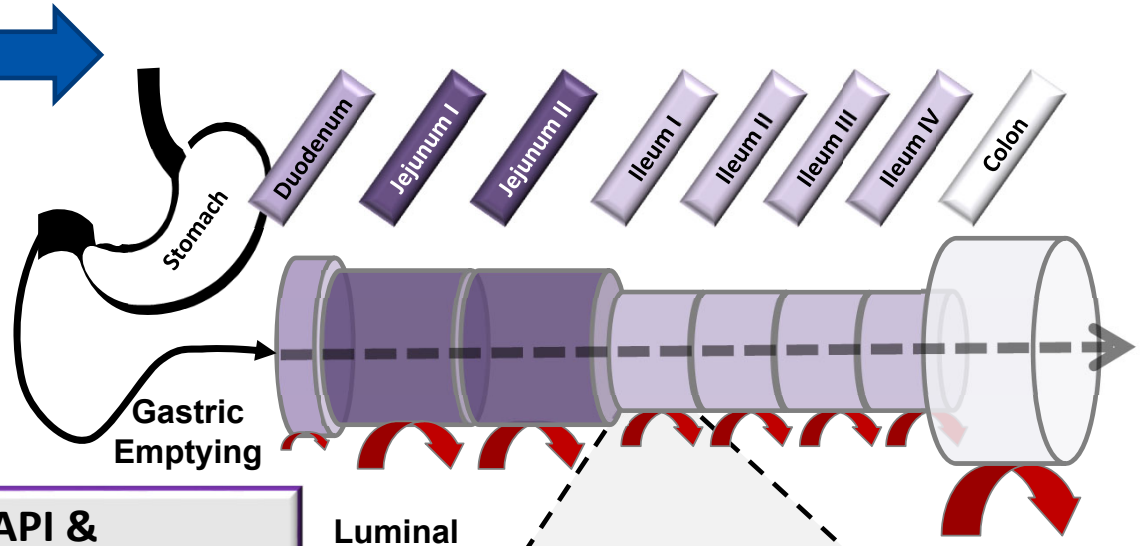
Model/Map
(Showing What Goes Where)



Master File
(Adjustment Capabilities)

ApplicationData
(Showing Functionality)

Drug/Formulation *Vs* Systems

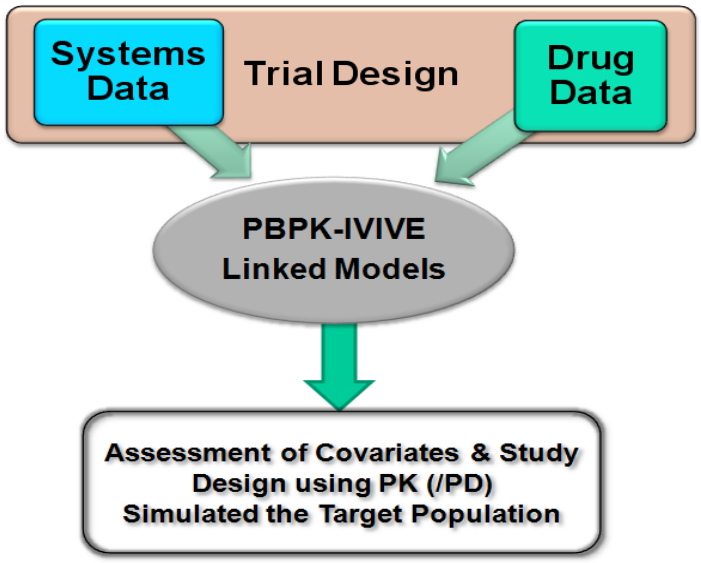


STATE OF THE ART — nature publishing group

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]

Schematic Representation of Workflow



Attributes of API & Formulation:

Disintegration; De-aggregation; Solubility; Dissolution; Precipitation; Super-saturation; Permeability; Gut Wall Metabolism; Intra-lumenal Degradation; etc.

Attributes of Physiology:

pH; Bile Salts; Bicarbonate; Fluid volume & dynamic; Enzyme & Transporter Activity; Blood Flow; etc.

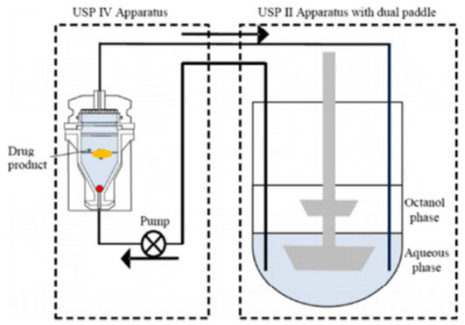
Journal of Pharmaceutical Innovation (2020) 15:296–317
https://doi.org/10.1007/s12247-019-09392-6

REVIEW ARTICLE

Check for updates

Advances in In Vivo Predictive Dissolution Testing of Solid Oral Formulations: How Closer to In Vivo Performance?

Meera Shrivas [1] · Dignesh Khunt [1] · Meenakshee Shrivas [1] · Manisha Choudhari [1] · Rajeshwari Rathod [1] · Manju Misra [1]



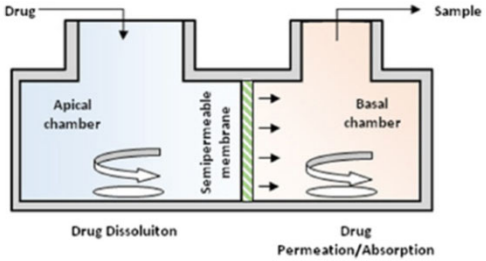
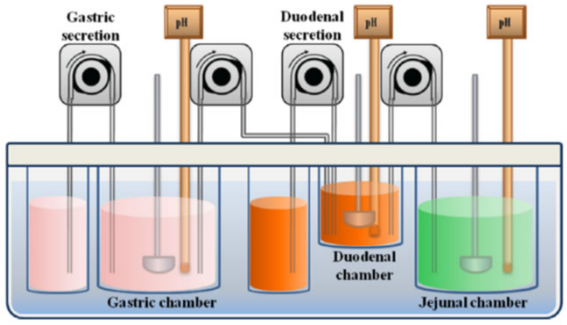


Fig. 1 Schematic of the dissolution/permeation (D/P) system

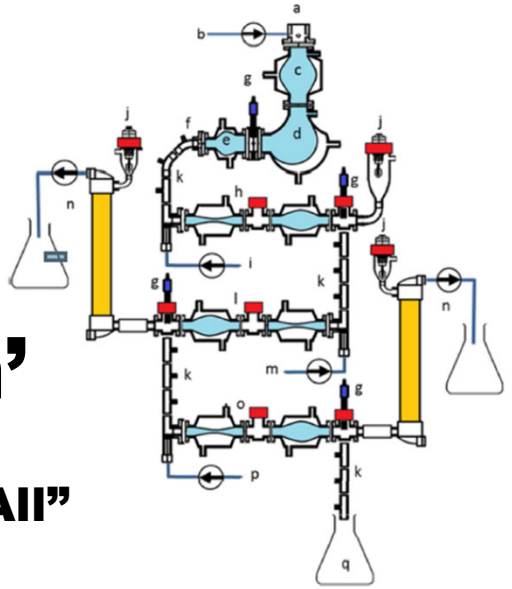


Systems Approach Is Incompatible with Common Philosophy of "Predictive Dissolution"!

There is

NO UNIQUE 'Predictive Dissolution'

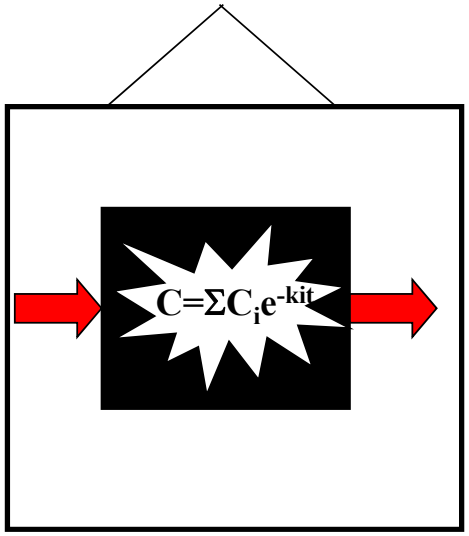
That Caters for 'All' Drug/Formulations in "All" Clinical Conditions!



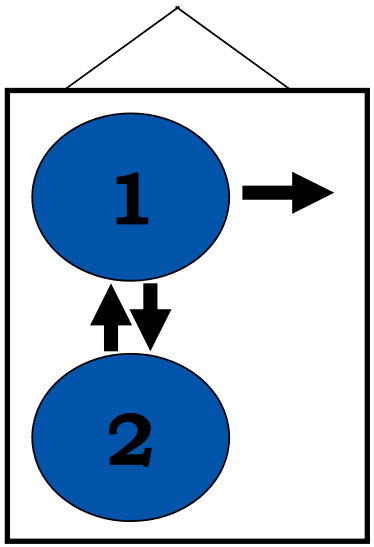
A Gallery of Models

Courtesy of Geoff Tucker
Basic PK Course

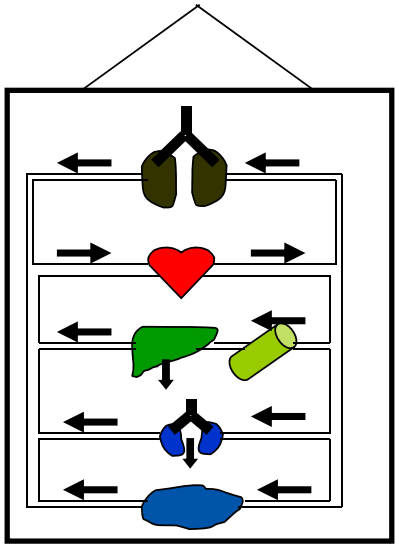
Courtesy of Andrzej Kierzek
QSP Modelling, Certara



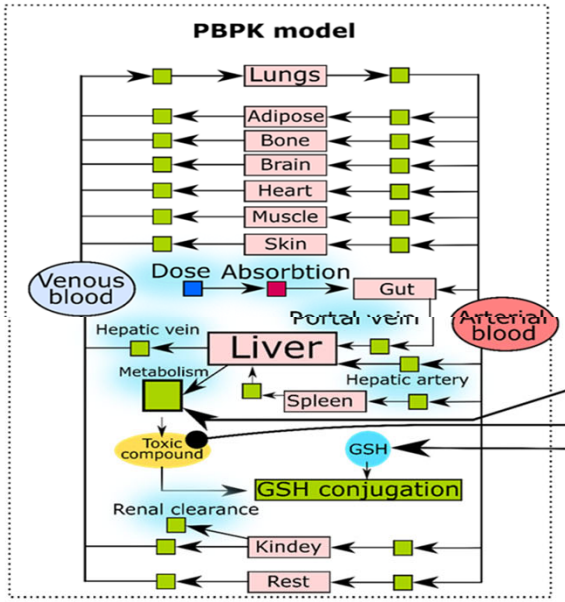
Empirical

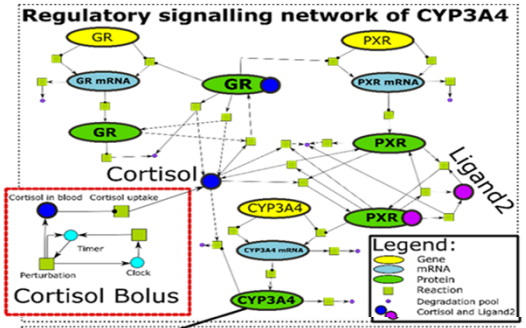


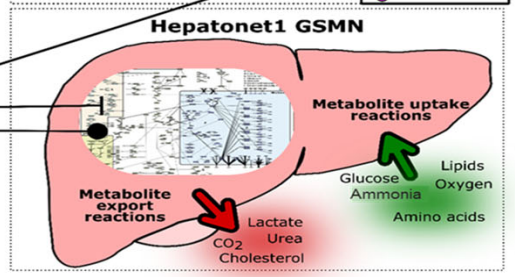
Compartmental



Physiological







Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 732–746; doi:10.1002/psp4.12230

TUTORIAL

Integration of Genome Scale Metabolic Networks and Gene Regulation of Metabolic Enzymes With Physiologically Based Pharmacokinetics

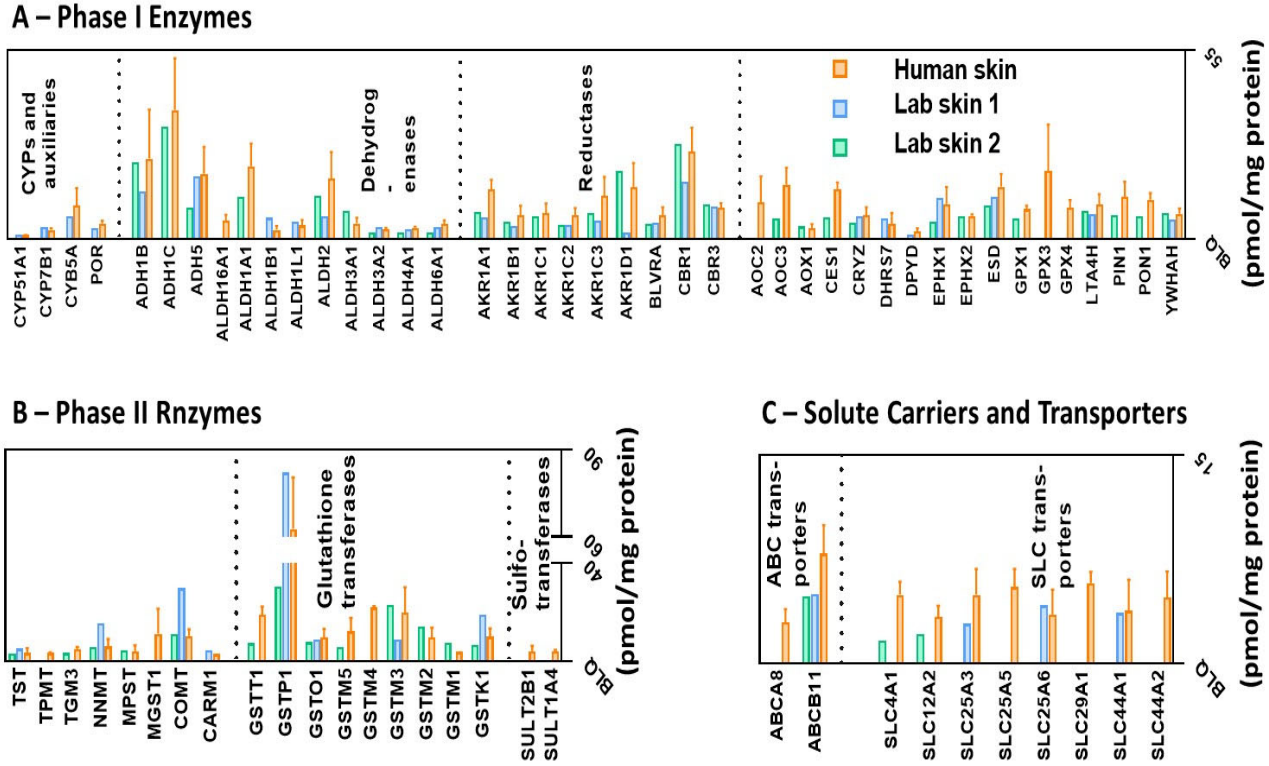
Elaina M. Maldonado[1], Vytautas Leoncikas[2], Ciarán P. Fisher[3], J. Bernadette Moore[1,4], Nick J. Plant[5] and Andrzej M. Kierzek[1,2]*

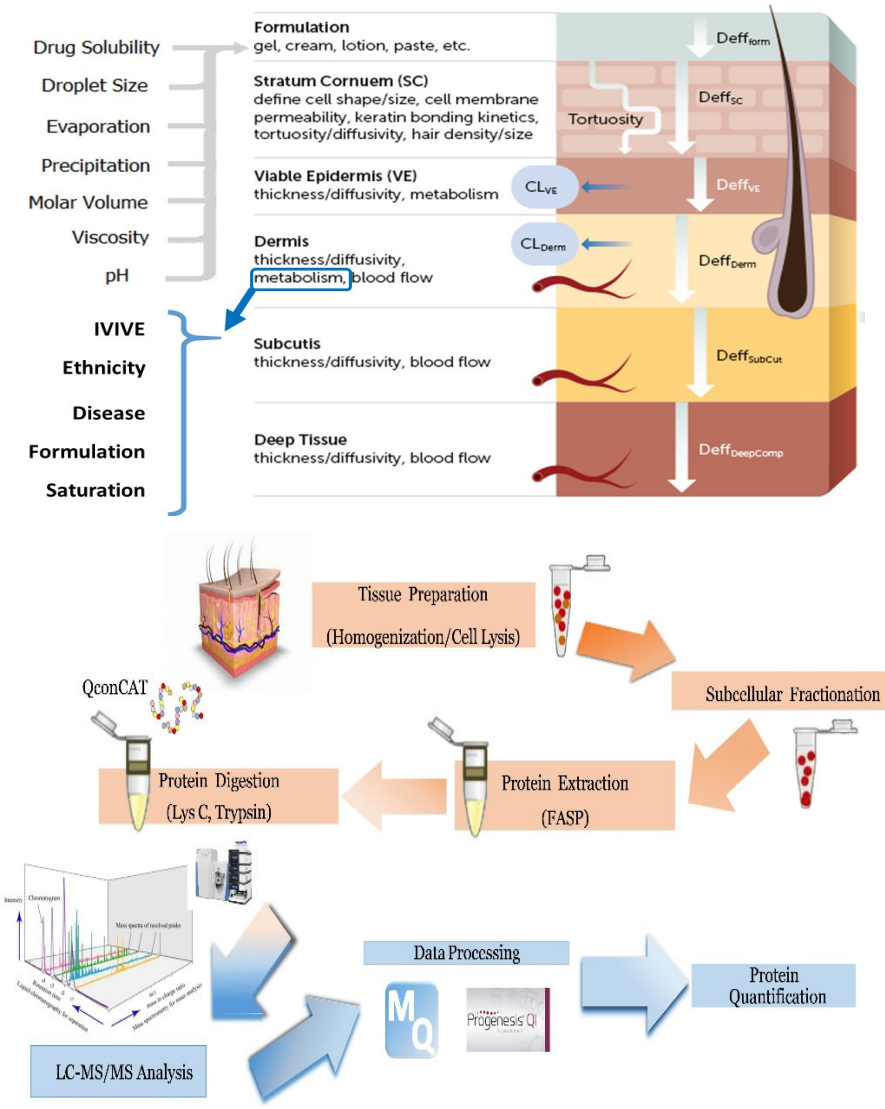
MASTER MODEL FILE: Scaffold for Biology/Physiology Data in Health and Disease

1521-009X/49/1/39–52$35.00
Drug Metabolism and Disposition
Copyright © 2020 by The American Society for Pharmacology and Experimental Therapeutics
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





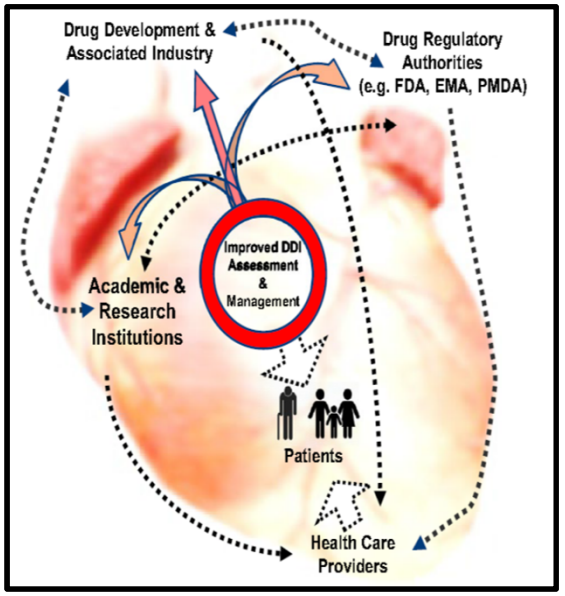
Sponsors of Model Master Files (Platforms & Associated Databases)

- Responsible for creation and ***continuous*** maintenance & enhancement of the platform and associated databases
- Unless supported by governments via ***public tax***, or via ***crowd funding*** / ***charities***, these will be ***private companies*** investing for financial benefit

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

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

- ***Collaboration*** **with beneficiaries at the heart of the matter**

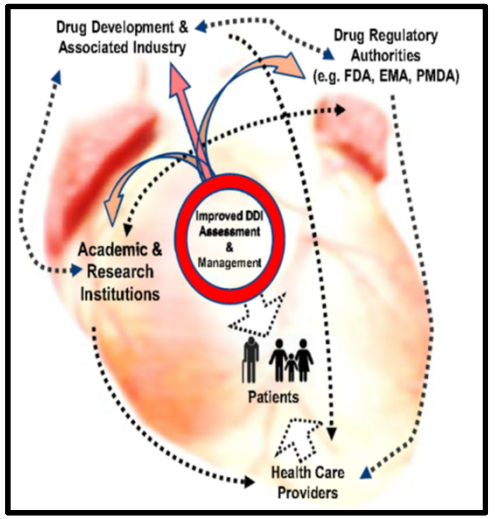


Beneficiaries of Model Master Files (MMF)

- ***Patients*** are the ultimate beneficiaries via access to affordable/safe drugs faster
  (this is not *entire* population to justify tax subsidies for MMF)
- ***Drug companies*** via faster development associated with financial gains
- ***Consultants*** (individual/firm) offering commercial services on applications
- ***Software providers*** of platforms if successful in a competitive free market
- ***Regulatory organisations*** through streamlining the assessment process

- **Beware of**
  Mixing the Roles
  &
  consequential ectopic beats leading to cardiac arrest!

(Judge, Jury, State, Lawyer, Defendant, Witness, Police, …. all in mix)



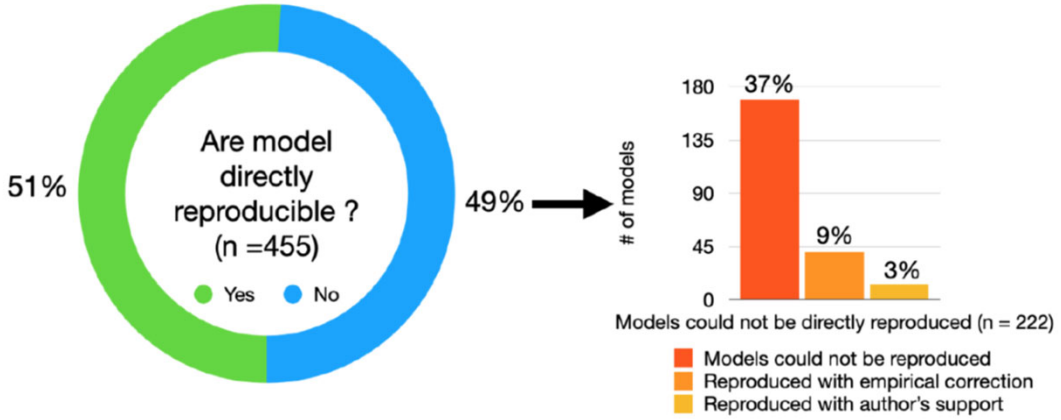
Counter-Intuitive Nature of Open Source-Code Models:

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



"Open"

Sounds Nice & Positive!

BUT NOT SO

If we apply it to safe place for keeping precious posessions:

"Easily Accessible"

&

"Unsecure"

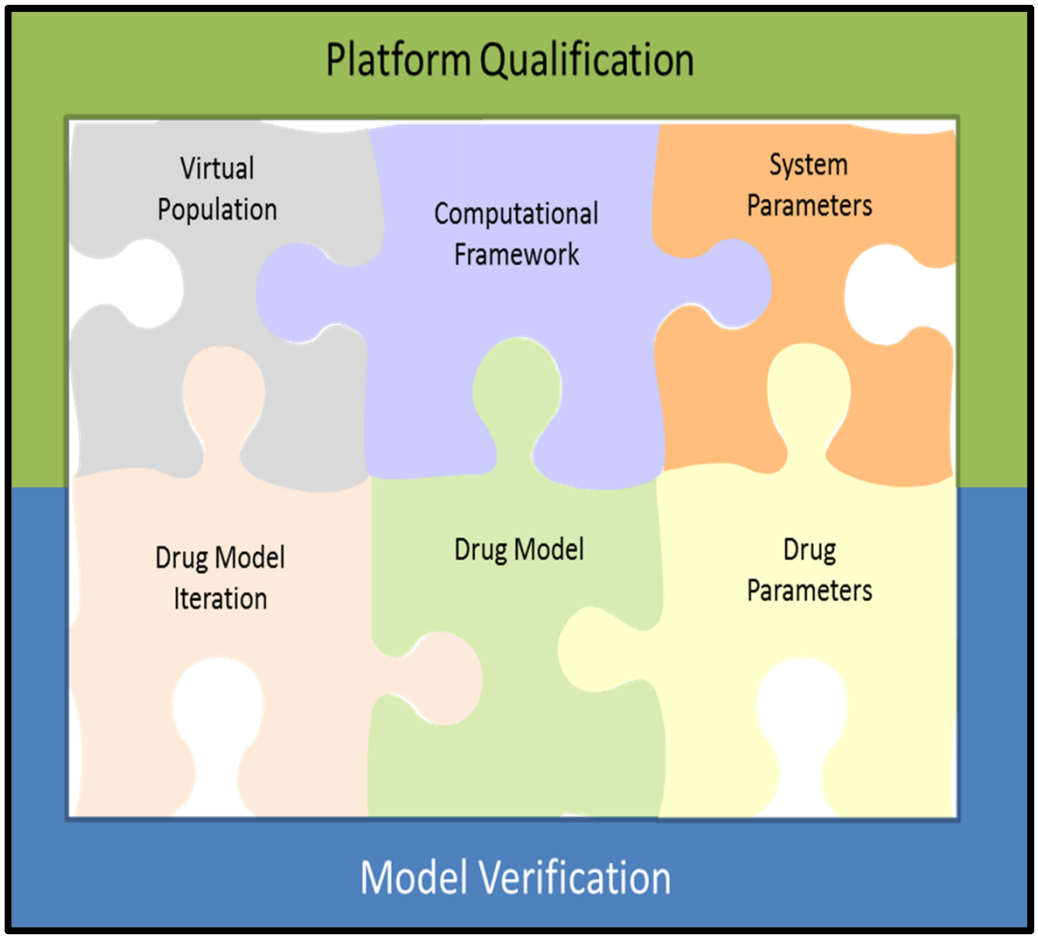
Hence

"Vulnerable"

to

"Adulteration"

A Consortium Approach: Platform *vs* Model



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

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]

A case example for MMF as **PBPK Package** for submission to regulatory agencies.

Green Frame - The PBPK platform

Undergo qualification only once and re-used for other cases;

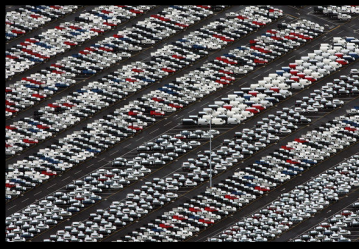
Blue Frame - The PBPK Component Files

Undergo verification for each submission.

Lateral Expansion / Wider Use of Mechanistic Multi-Layer Models

Non-Open-Source/Commercial Platforms Played a *'significant'* Role:

Research Frontier → Routine Scaled Up Usage

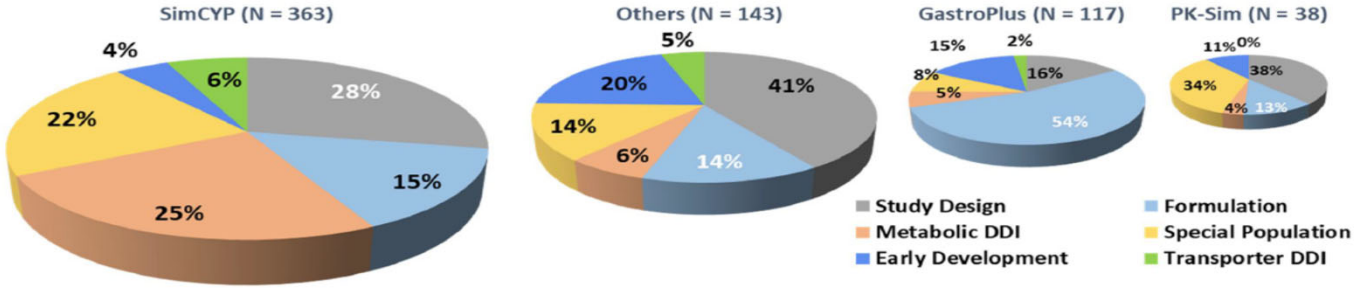


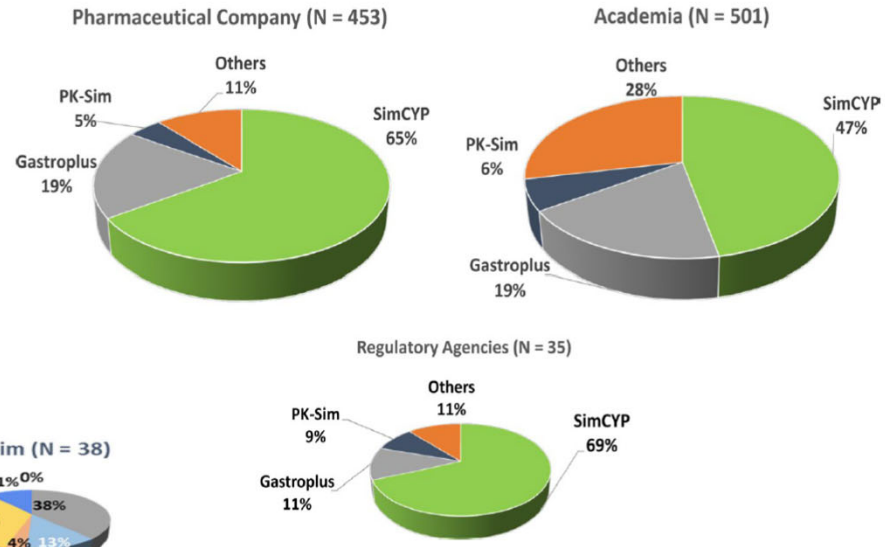
'Toys for Big Boys!' is replaced by / leads to creation of 'Modelling for All'

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

Rostami-Hodjegan & Bois (2021)
CPT Pharmacometrics Syst.Pharmacol. 2021;00:1–8.

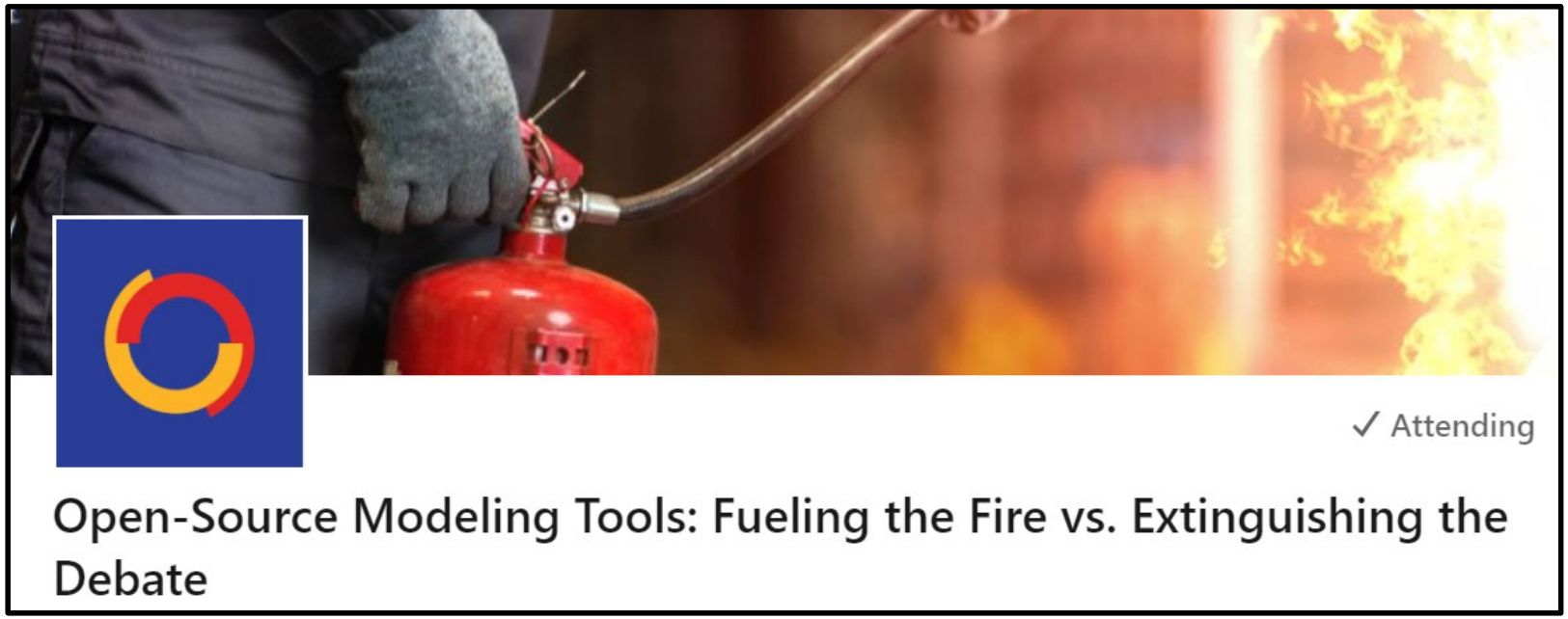
Physiological-based pharmacokinetic modeling trends in pharmaceutical drug development over the last 20-years; in-depth analysis of applications, organizations, and platforms





El-Khateeb et al. (2021)
Biopharm. Drug Dispos. 42:107–117.

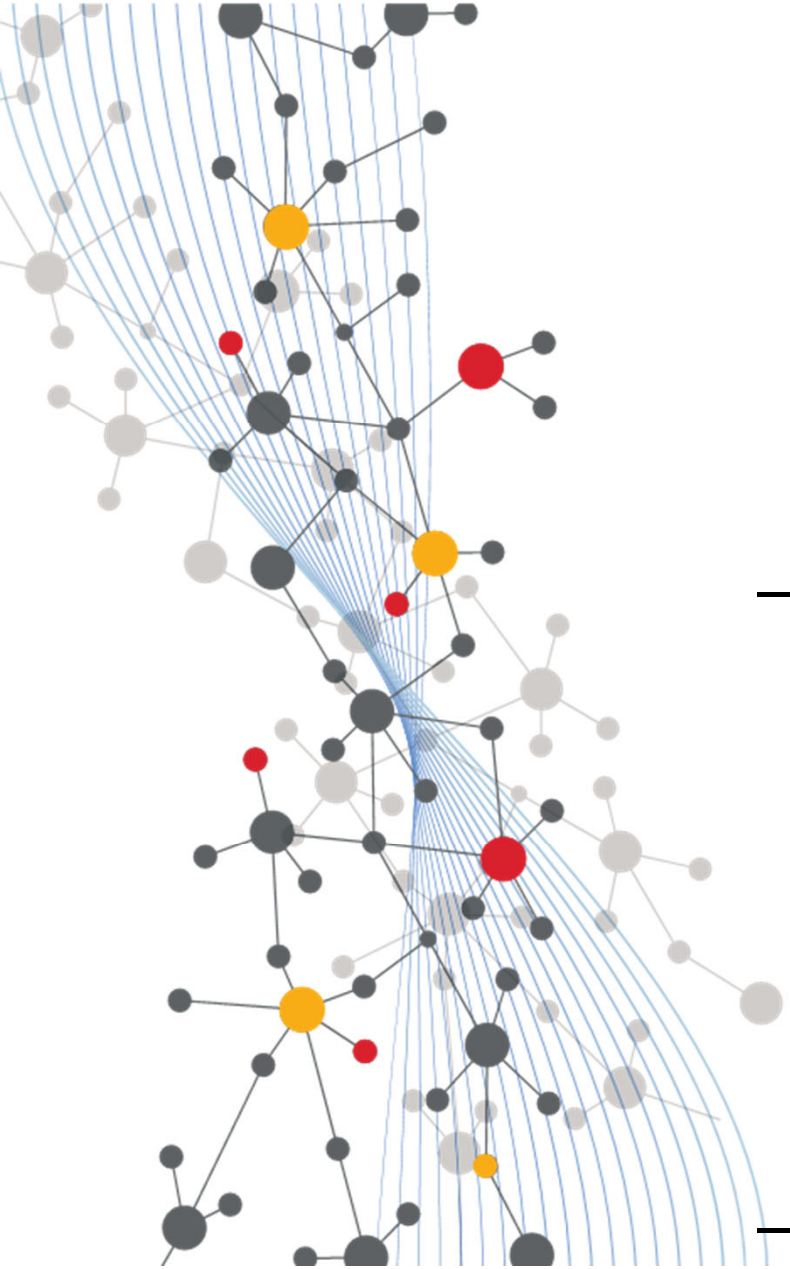
For Those Who Are Interested In Further Information



YouTube

A One Hour Interview - Available on YouTube at the Following Link:

https://youtu.be/gEnDrKiMS50



Topic for the Next 3 Minutes

A Case Example
The Need
for

MMF
(PLATFORM & DTATABASE)

Virtual Bioequivalence
(VBE)
&
Assigning Within-Subject Variability
(WSV)
During Modelling and Simulations
(M&S)

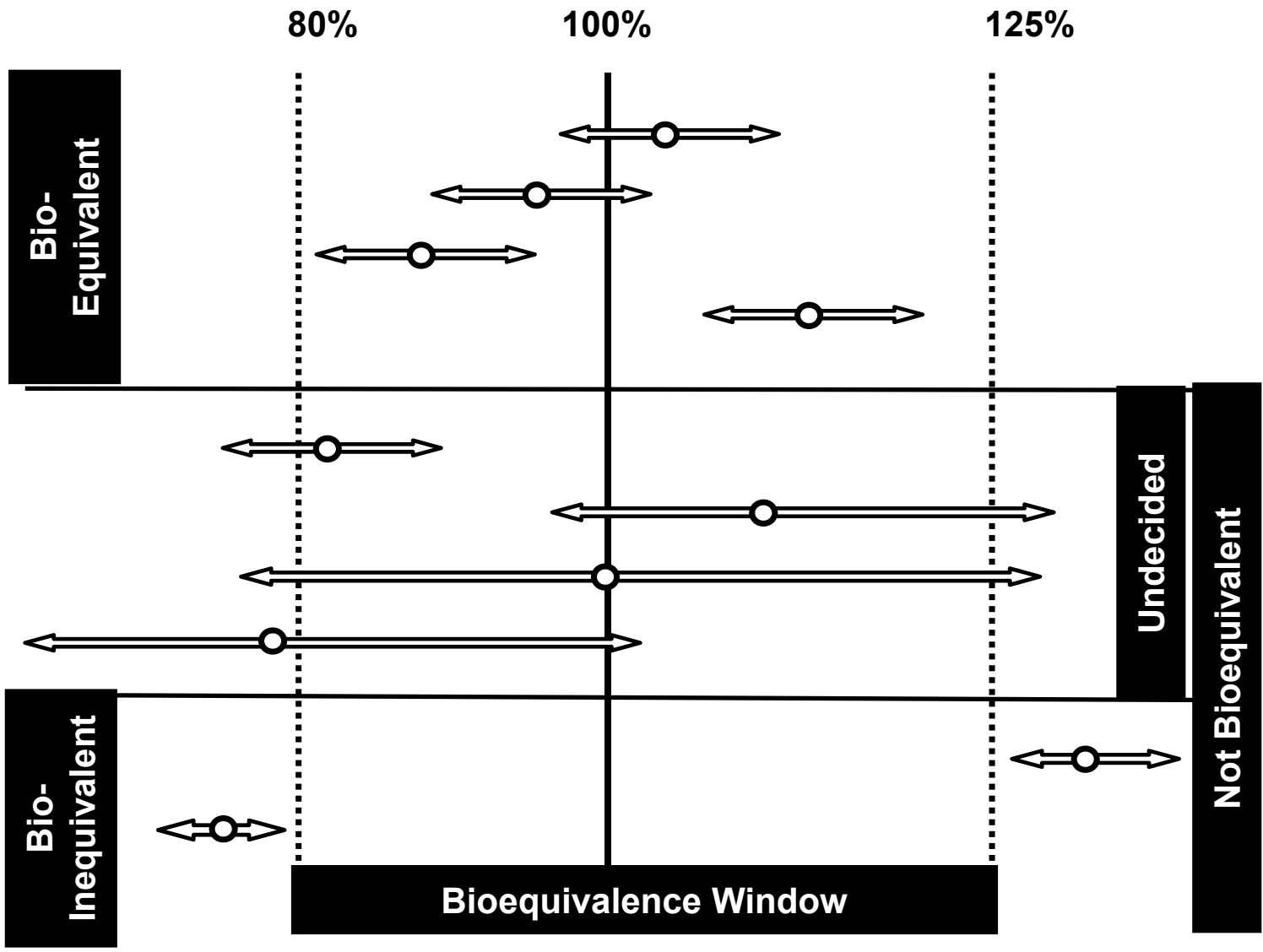
Cross-Over Design Protects against Biased Estimates of Relative BE for:

MEAN

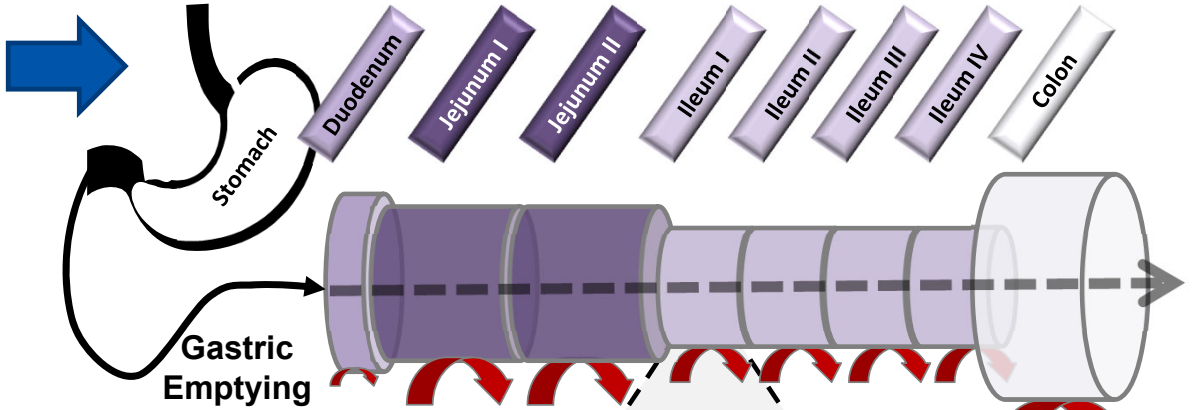
However, BE Studies are Sensitive to Inter-occasion Variability (IOV)/Within-Subject Variability (WSV)/Intra-Individual Variability which Influence the:

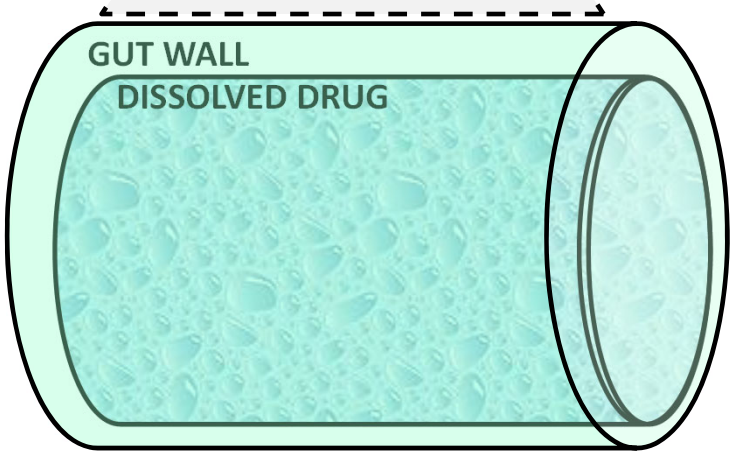
CONFIDENCE INTERVAL

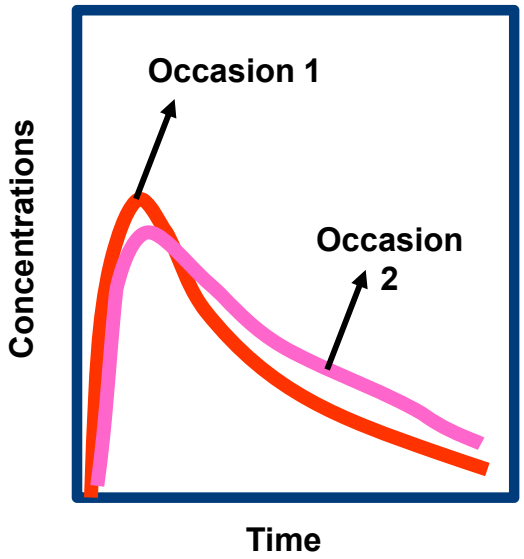
Bego *et al.* 2021, Under Review



Bego *et al.* 2021, Under Review







Attributes of API & Formulation:

Disintegration; De-aggregation; Solubility; Dissolution; Precipitation; Super-saturation; Permeability; Gut Wall Metabolism; Intra-lumenal Degradation; etc.

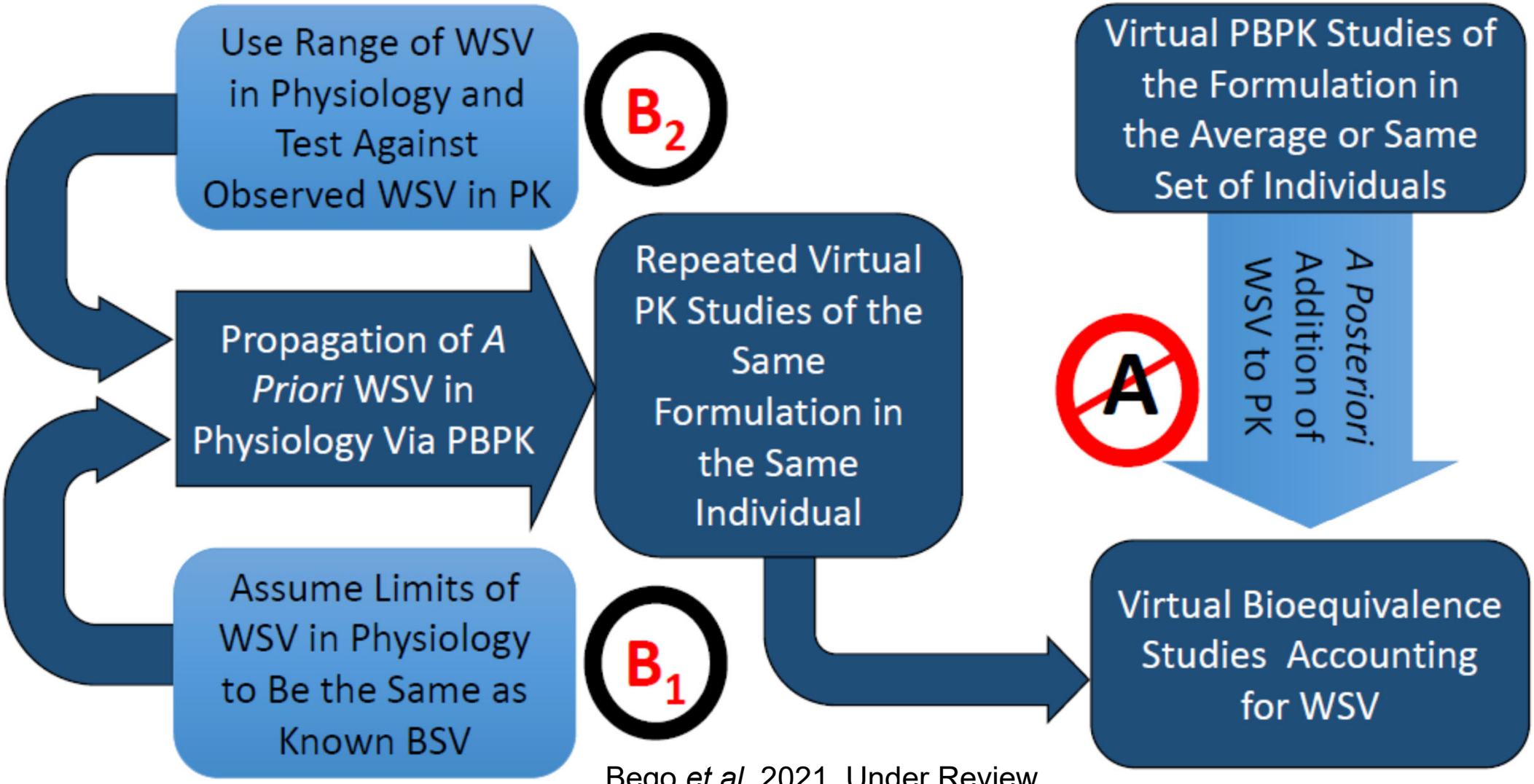
WSV in Physiology:

pH; Bile Salts; Bicarbonate; Fluid; Enzyme & Transporter Activity; Blood Flow; etc.

Observed WSV in Pharmacokinetics:

C_{max}; T_{max}, AUC; K_{el}; CL; etc.

Workflows of VBE Studies Accounting for WSV



Bego *et al.* 2021, Under Review

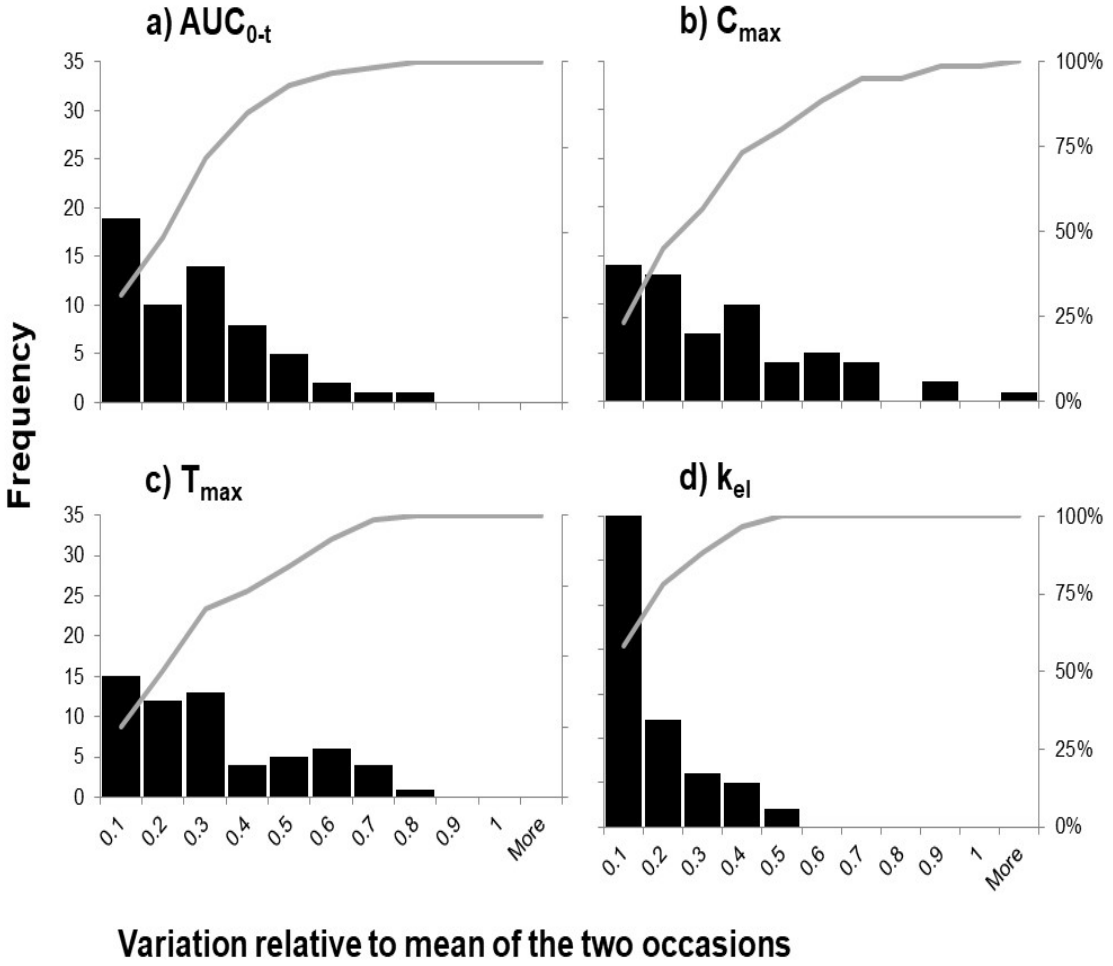
Sets of Hypothetical WSV in Physiological Parameters of GI Tract

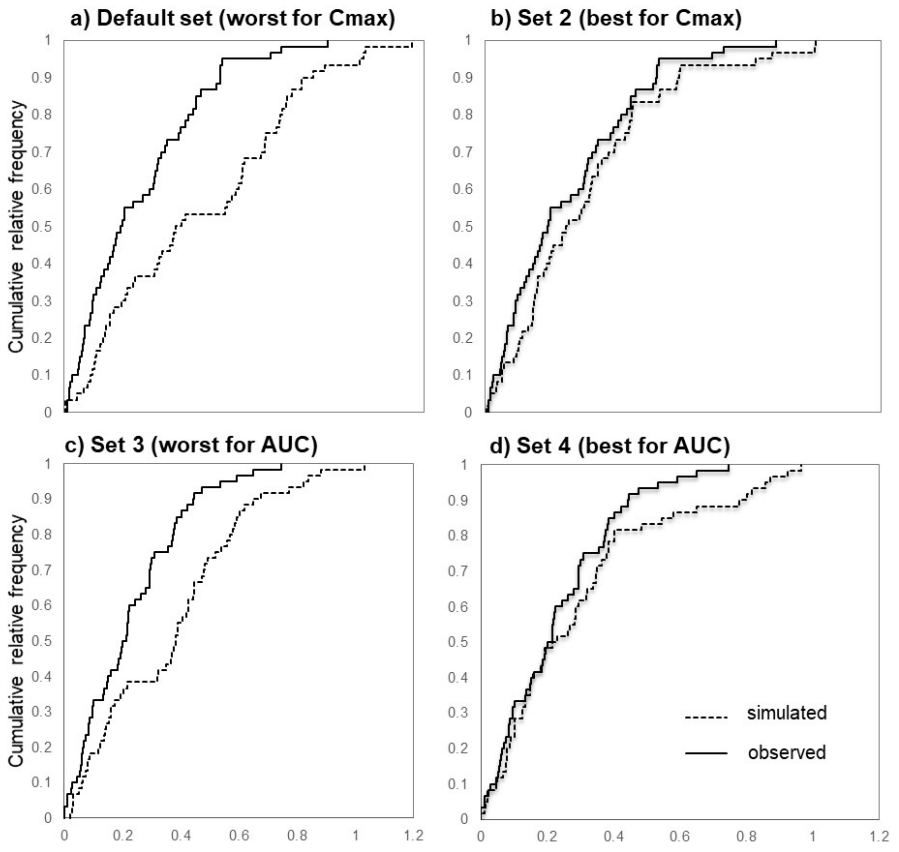
Table 2 Different sets of WSV in GI physiology investigated

Physiological Parameters - WSV CV%	Default	Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Set 7	Set 8	Set 9	Set 10	Set 11	Set 12	Set 13	Set 14
Gastric MRT(h)	38	19	19	19	25	30	25	25	30	25	19	38	38	38	19
Small Intestine MRT (h)	30	15	15	15	10	10	10	20	15	10	15	15	15	30	15
Colon MRT (h)	30	30	30	30	30	20	20	30	30	30	30	30	30	30	30
Duodenum pH Fasted	16	16	16	8	16	8	10	16	10	16	16	16	16	16	Dy
Duodenum Bile Salt Conc Fasted	97	97	49	97	70	97	70	49	49	49	49	97	97	97	49
Jejunum I pH Fasted	13	13	13	7	13	7	10	13	5	13	13	13	13	13	Dy
Jejunum I Bile Salt Conc Fasted	100	100	50	100	70	100	70	50	50	50	50	100	100	100	50
Jejunum II pH Fasted	11	11	11	6	11	6	10	11	5	11	11	11	11	11	Dy
Jejunum II Bile Salt Conc Fasted	42	42	21	42	30	30	30	21	21	21	21	21	42	21	21

CV% differing from the default (BSV) value are highlighted blue. CV% for volume of water administered was set to 1%, initial volume of stomach fluid at 30%, stomach pH at 38% and drug clearance to 5% in all sets except Set 10 (where CV% in CL was set to 0%). CVs for liver and brain volume and kidney weight were set to zero. Dy=dynamic (option in the Simcyp simulator)

Assessing Incompatibility of Assigned WSV in Physiological Parameters Using Comparison with Observed WSV of PK





Bego *et al.* 2021, Under Review

Exclusion of Certain Sets of WSV in Physiological Parameters of GI Tract hat Are Incompatible with PK observations for WSV.

Table - Comparison of simulated *vs* observed intra-subject variability (Full set of individuals, Kolmogorov-Smirnov test)

Bego *et al.* 2021, Under Review

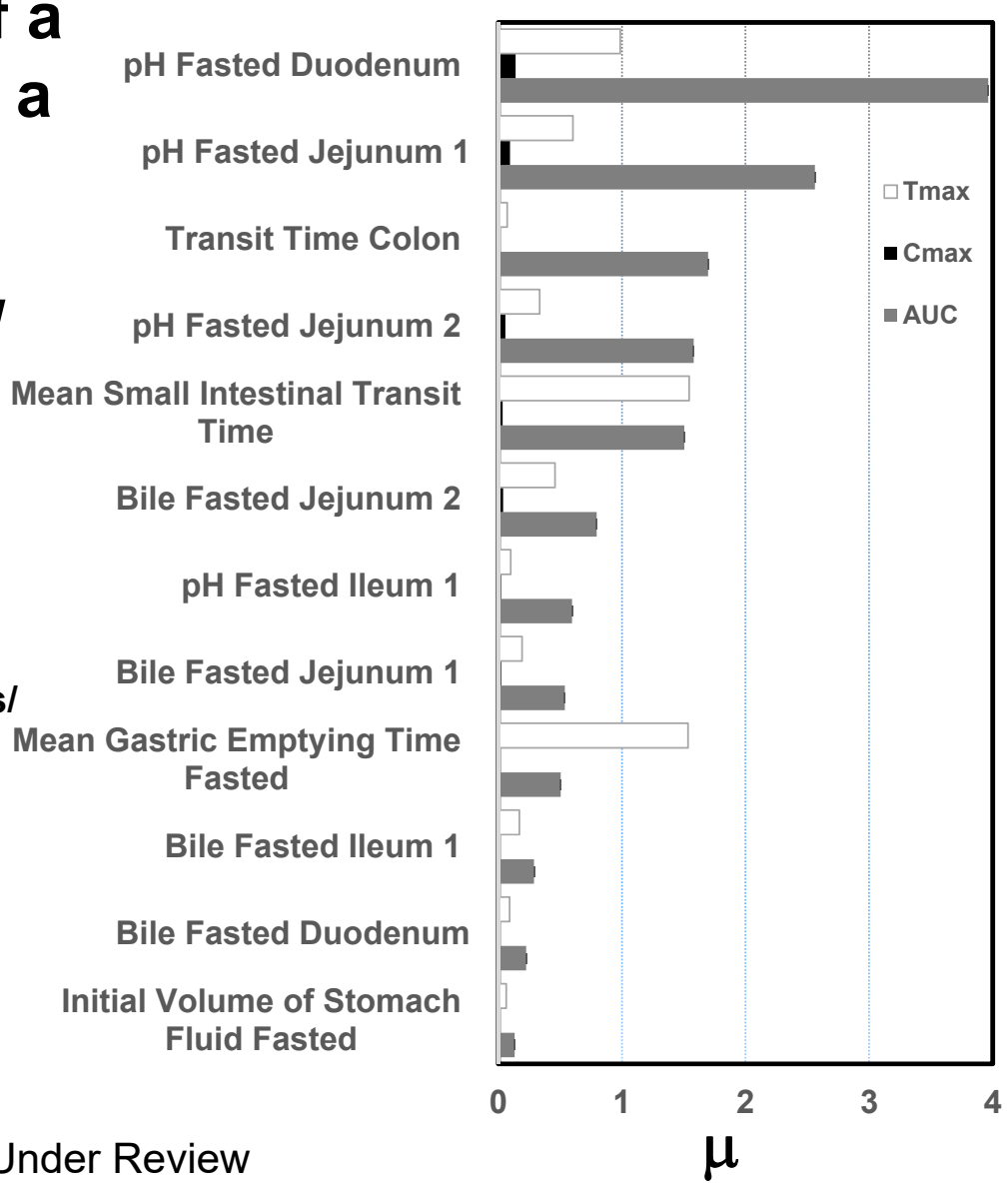
Observed vs Predicted Distributions (AUC, C_{max} and T_{max}) (Kolmogorov-Smirnov Test)						
SET	D statistic AUC	Similarity (Y/N)	D statistic Cmax	Similarity Y/N)	D statistic Tmax	Similarity (Y/N)
(default)	0.350	No	0.417	No	0.200	Yes
1	0.200	Yes	0.217	Yes	0.150	Yes
2	0.167	Yes	0.150	Yes	0.217	Yes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

WSV in physiology is independent of a given drug/formulation and same for a given condition
(unless they are pharmacologically acting on GI tract)

Despite being the same for all drugs/ formulations, some of WSV in physiology do not propagate to outcome for a some drugs/ formulations.
(hence, the requirement to run the calculations for several drugs/ formulations with different characteristics)

Global Sensitivity Analysis (GSA, Morris Method, Simcyp) as the absolute mean (μ*) values.

High μ* indicates a parameter with an important influence on the model output (AUC, C_{max} or T_{max}).



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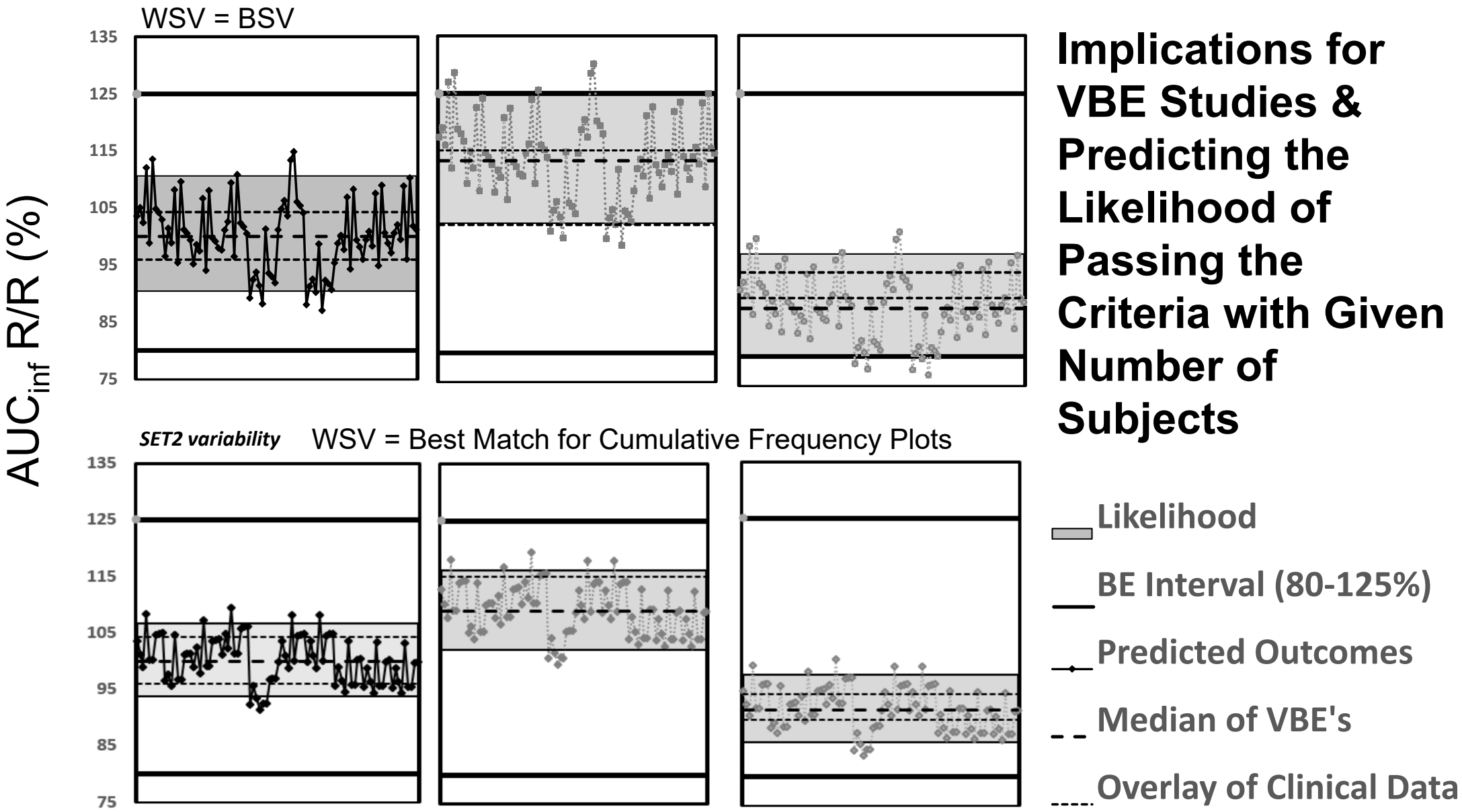

WSV = BSV
135
125
115
105
95
85
75
AUC$_{inf}$ R/R (%)
SET2 variability
WSV = Best Match for Cumulative Frequency Plots
135
125
115
105
95
85
75
Implications for VBE Studies & Predicting the Likelihood of Passing the Criteria with Given Number of Subjects
Likelihood
BE Interval (80-125%)
Predicted Outcomes
Median of VBE's
Overlay of Clinical Data

Relevance of Model Master File

Avoids Starting from Scratch!

by

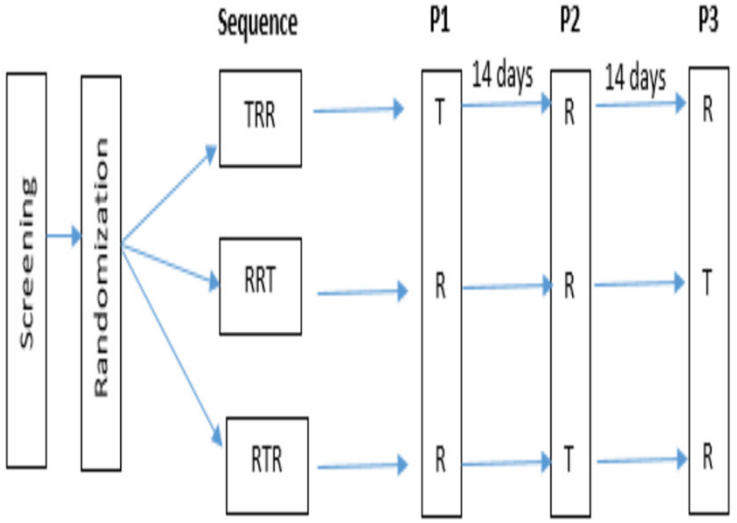
Accumulating *CONTINUOUS* Effort on Using Previous Studies on

VARIOUS DRUGS/FORMULATIONS

to

Gain Insight into

DRUG/FORMULATION-INDEPNDENT



WSV/IOV of Physiology as an Example:

Once Fully Resolved, This Can be Incorporated in Any User-Friendly Model Master File Specifically Built for

VBE