FDA-CRCG workshop:
Best Practices for Utilizing Modeling Approaches to Support Generic Product Development

27th - 28th October 2022

Model Reusability

"Model Master File Perspective"

Amin Rostami,

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

Lateral Expansion / Wider Use of Mechanistic Multi-Layer Models

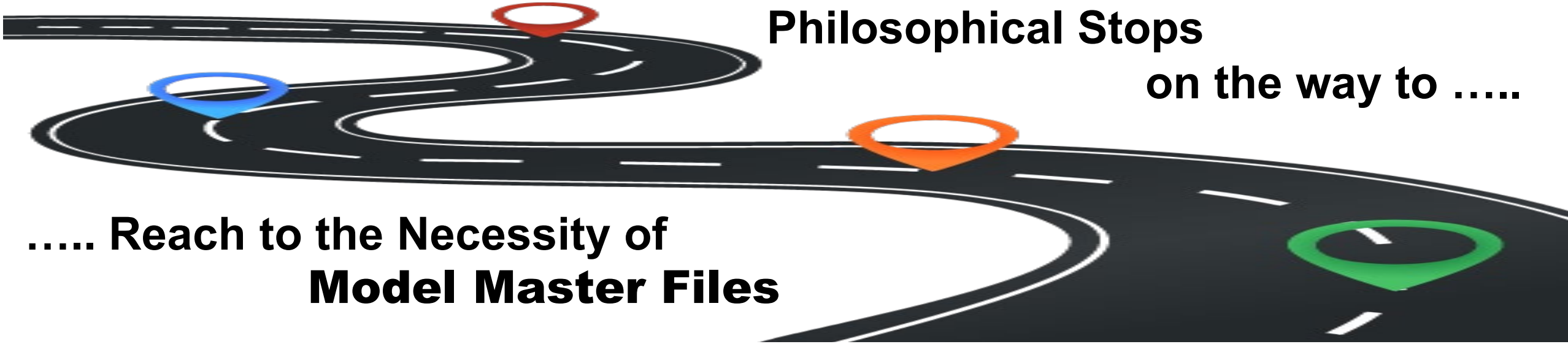
The Road for Natural Progression of Systems Model To

Model Master File

Research Frontier

Routine Scaled Up Usage

‘Toys for Big Boys!’ replaced by ‘Modelling by All for All’



Philosophical Stops on the way to …..

….. Reach to the Necessity of Model Master Files

STATE OF THE ART

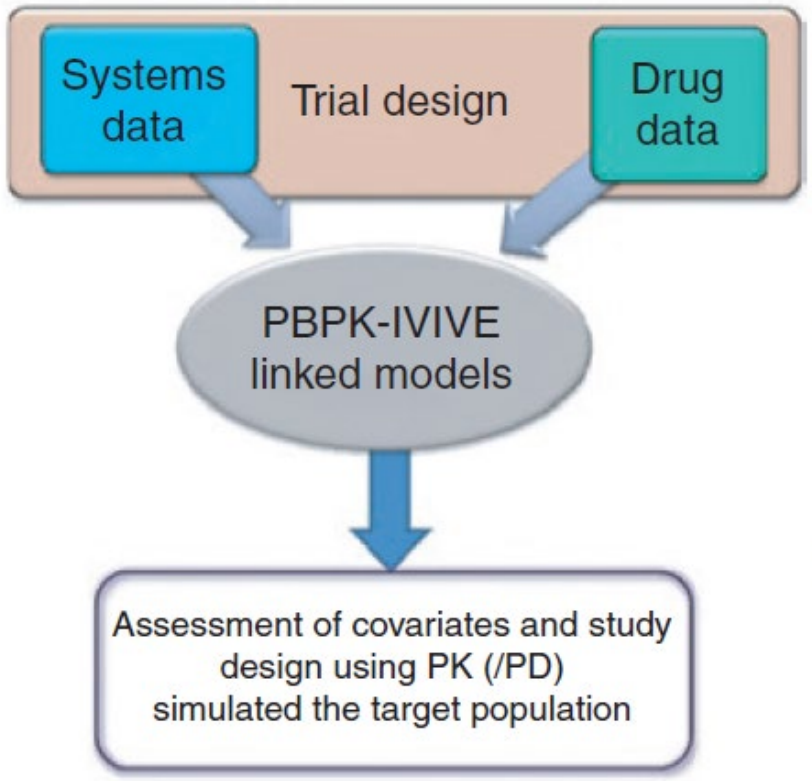
Clin Pharm Ther 2012 - 92 (1): 50-61

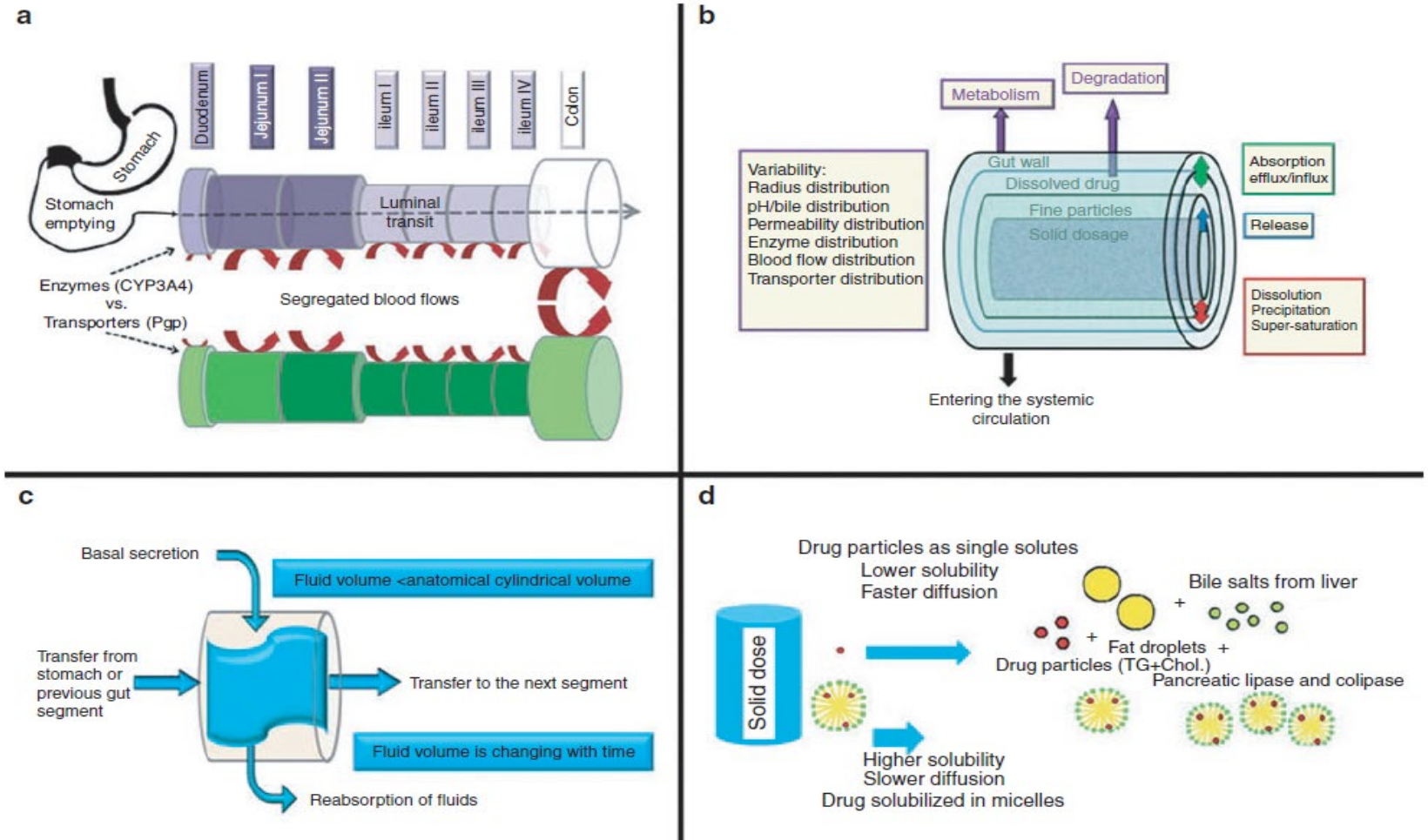
nature publishing group

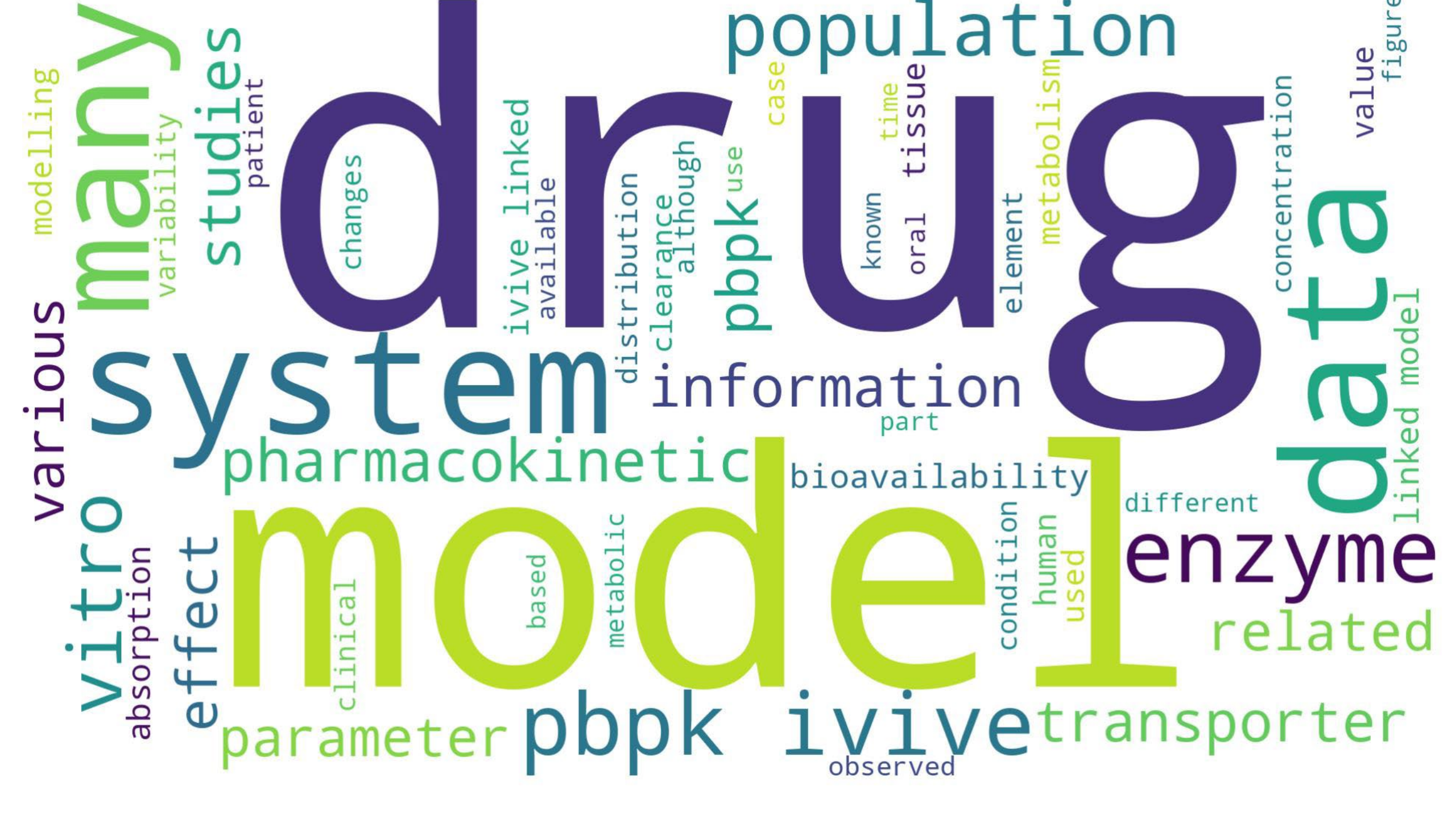
Physiologically Based Pharmacokinetics Joined With *In Vitro–In Vivo* Extrapolation of ADME: A Marriage Under the Arch of Systems Pharmacology

A Rostami-Hodjegan[1,2]

Philosophical Stop No 1



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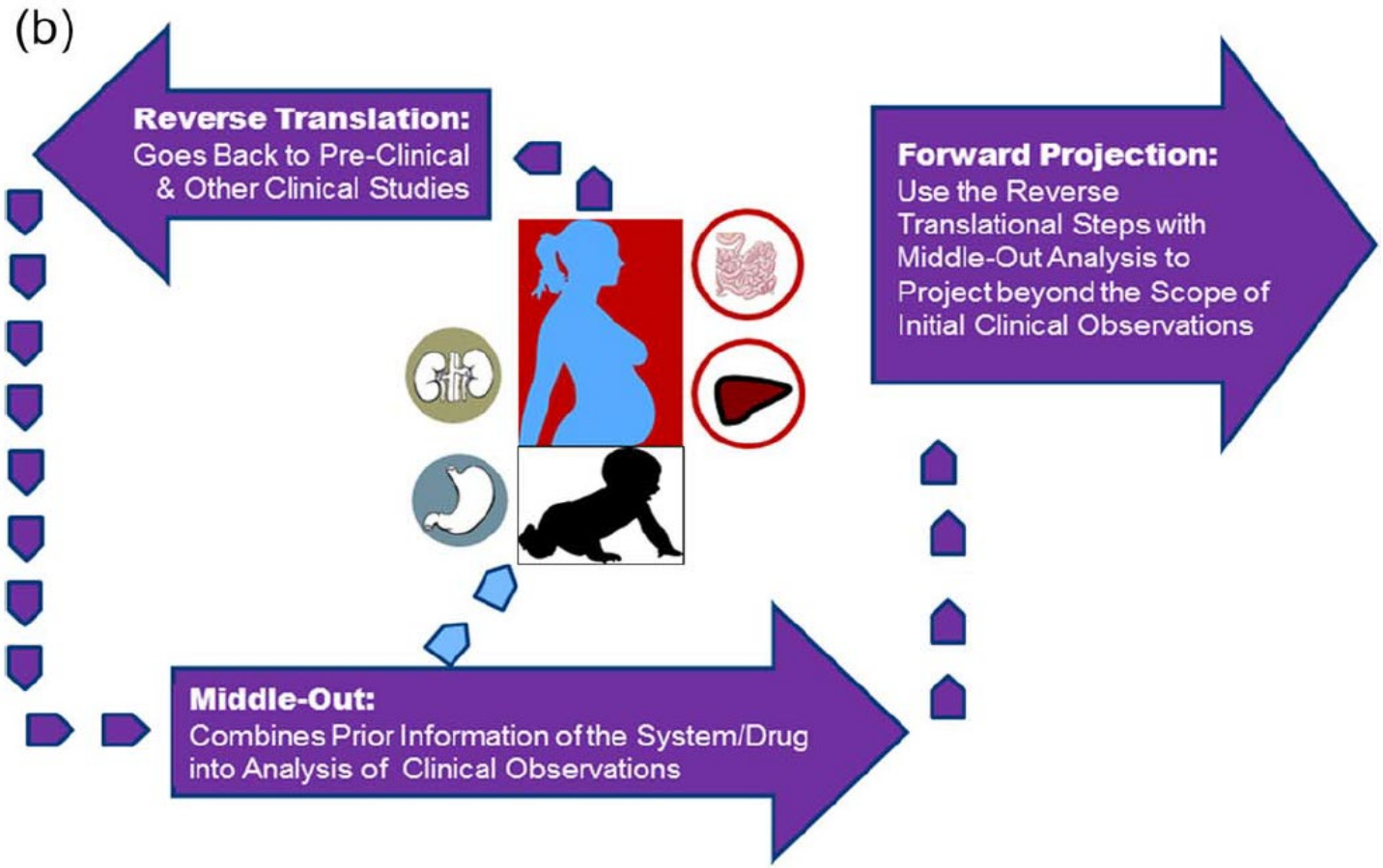
STATE OF THE ART

Clin Pharm Ther 2018 - 103 (2): 224-232

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

Amin Rostami-Hodjegan[1,2]

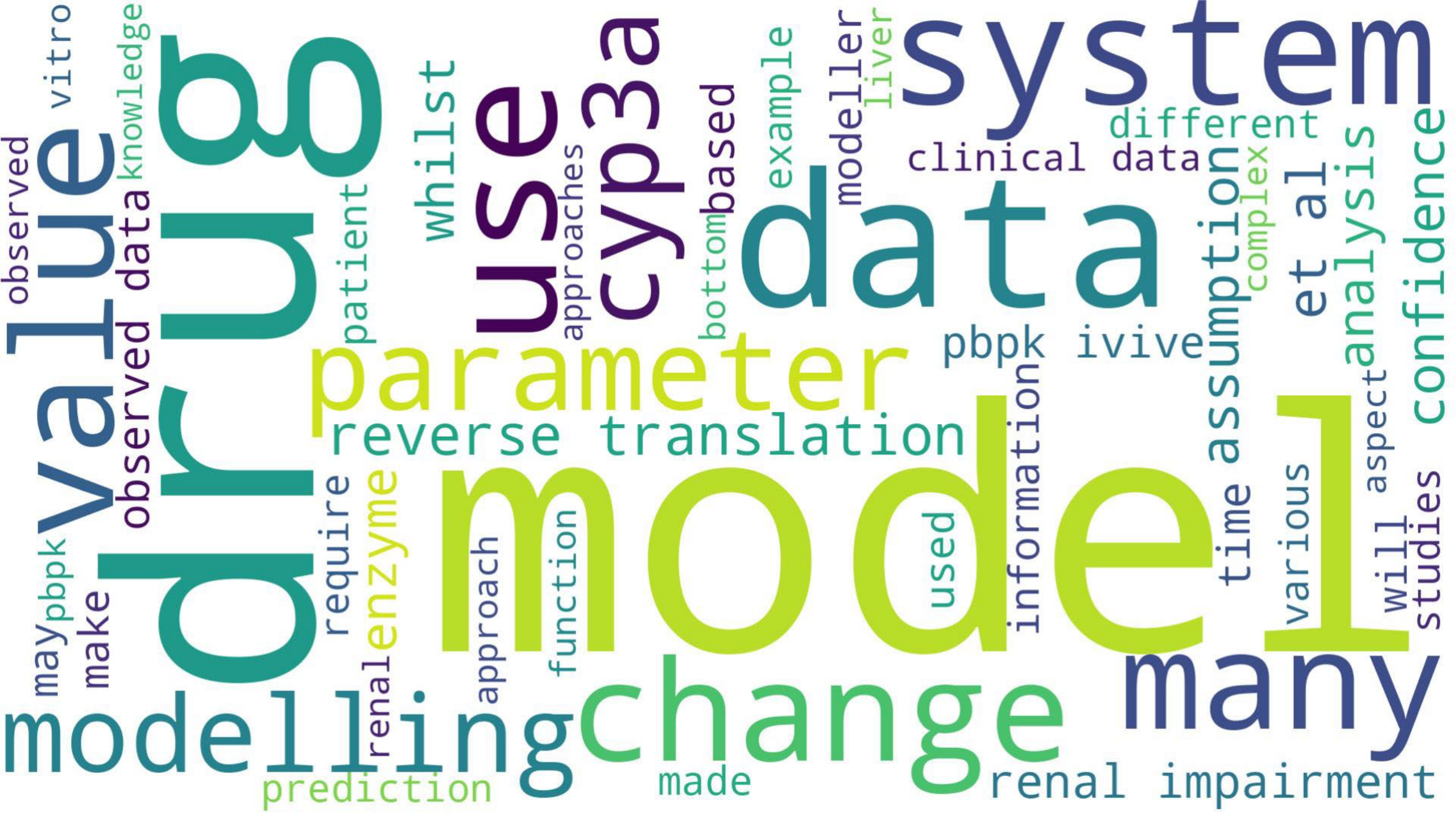


Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data

Nikolaos Tsamandouras,[1] Amin Rostami-Hodjegan[1,2] & Leon Aarons[1]

Br J Clin Pharmacol 2014 -79 (1): 48-55

Philosophical Stop No 2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made
renal impairment

DOI: 10.1002/psp4.12615

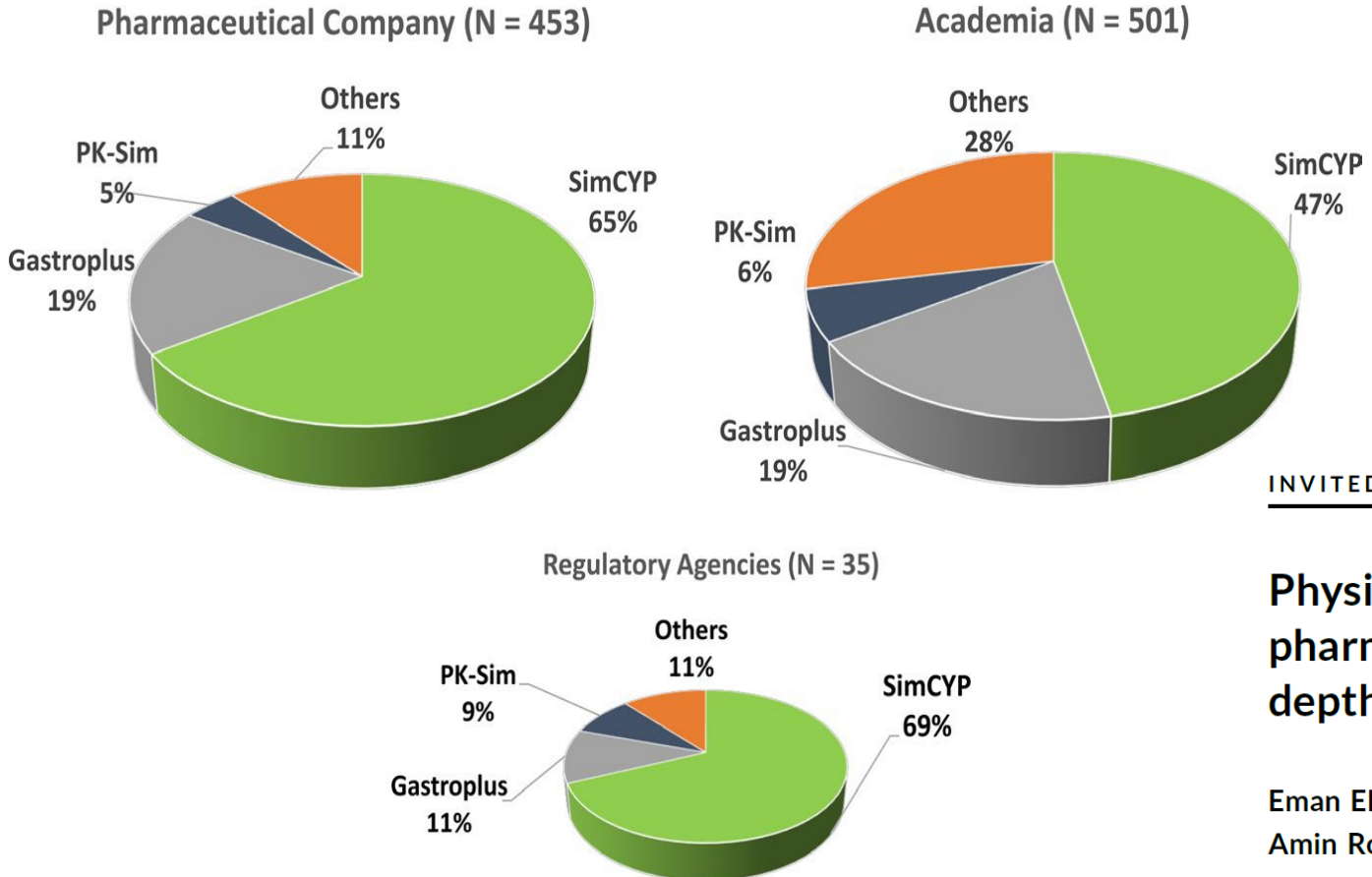
Philosophical Stop No 3

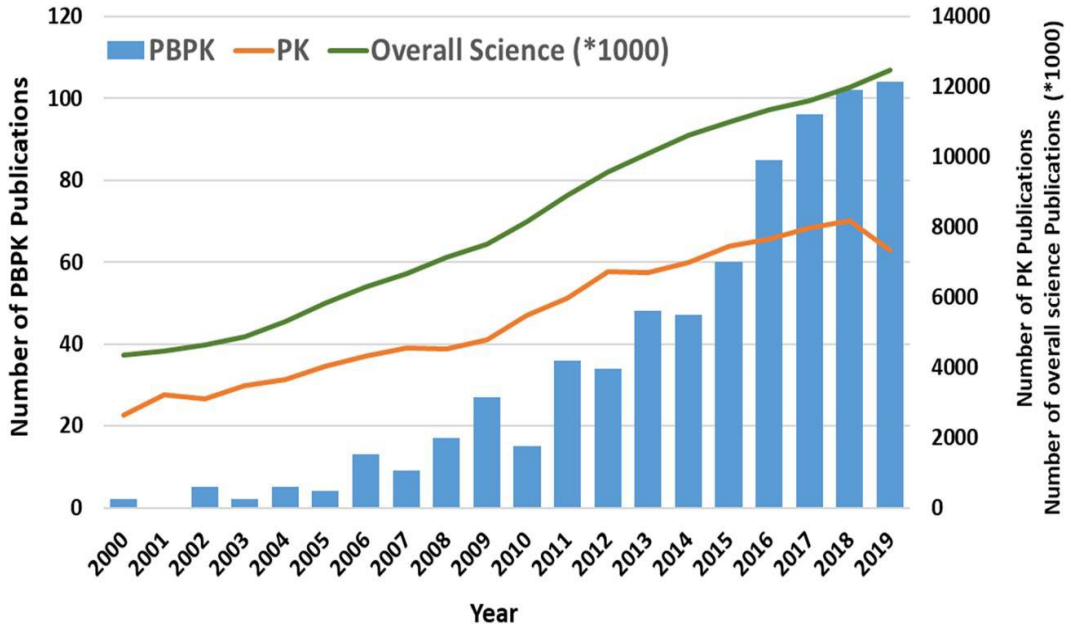
MINI-REVIEW

Pharmacometrics Syst. Pharmacol. 2021

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]





Biopharm Drug Dispos 2021 42: 107-117

WILEY

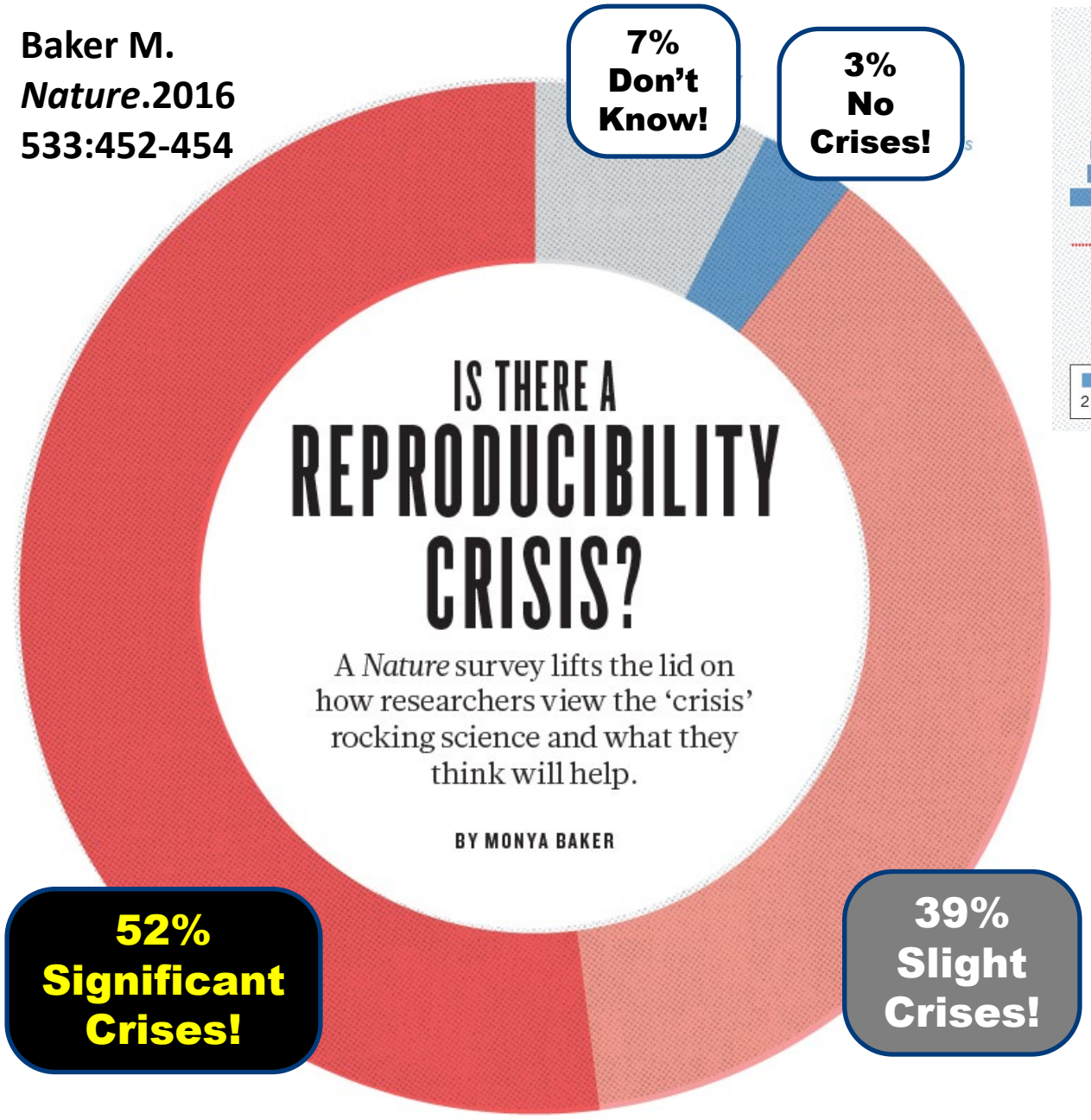
INVITED REVIEW

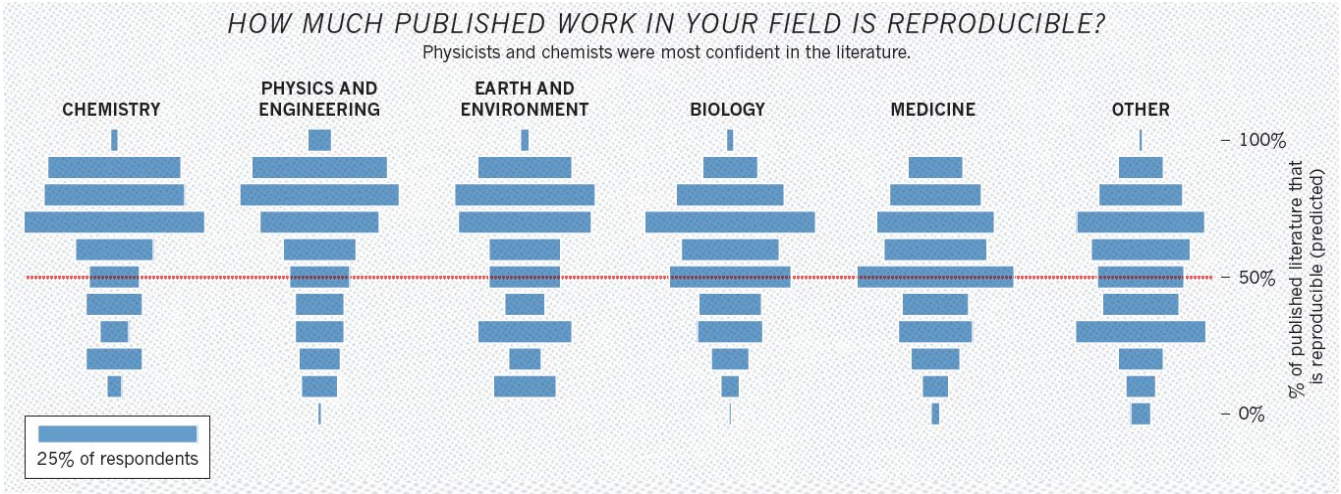
Physiological-based pharmacokinetic modeling trends in pharmaceutical drug development over the last 20-years; in-depth analysis of applications, organizations, and platforms

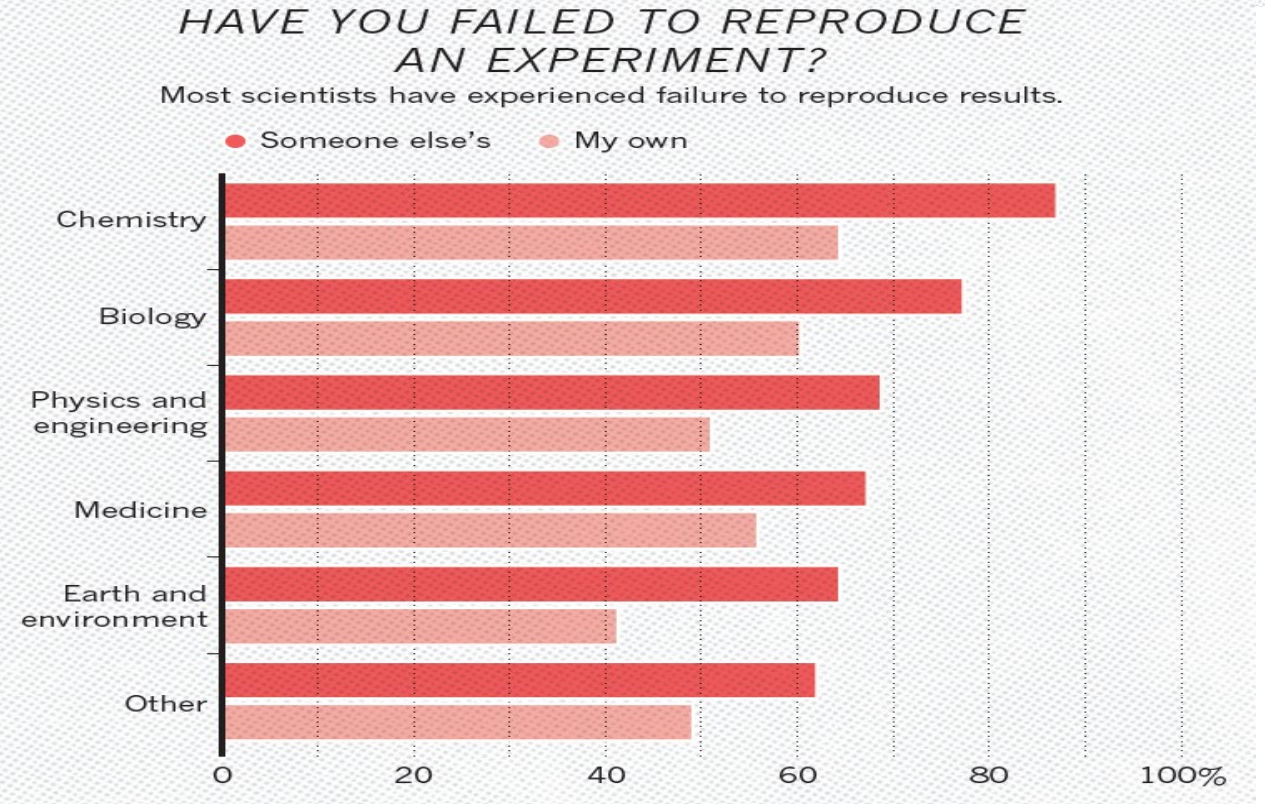
Eman El-Khateeb[1,2] | Susan Burkhill[3] | Susan Murby[1] | Hamza Amirat[1] | Amin Rostami-Hodjegan[1,3] | Amais Ahmad[1]

Trust in Scientific Outcomes: The Issue of Reproducibility

Baker M.
Nature.2016
533:452-454







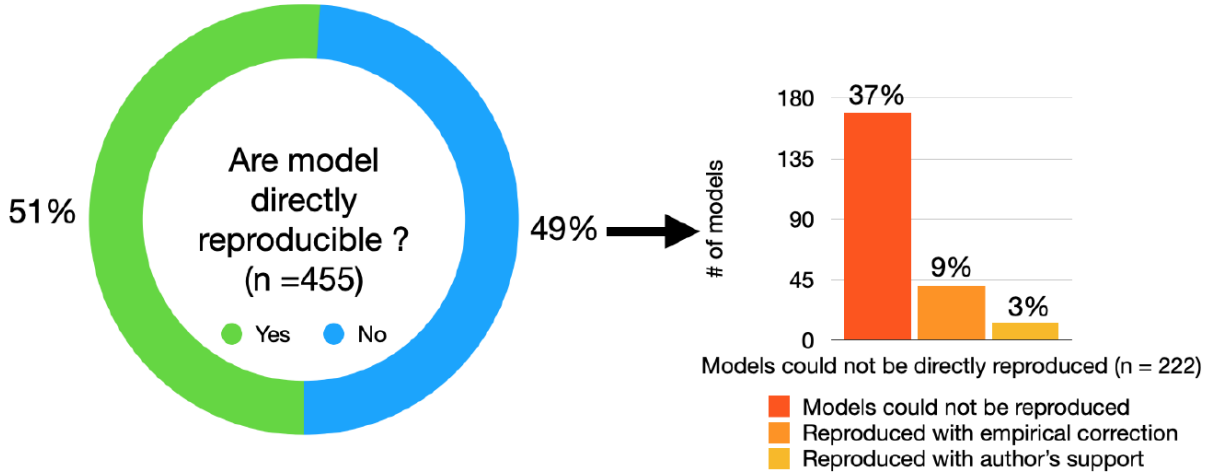
Counter-Intuitive Nature of Open Source-Code Models:

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 possessions:

"Easily Accessible"

&

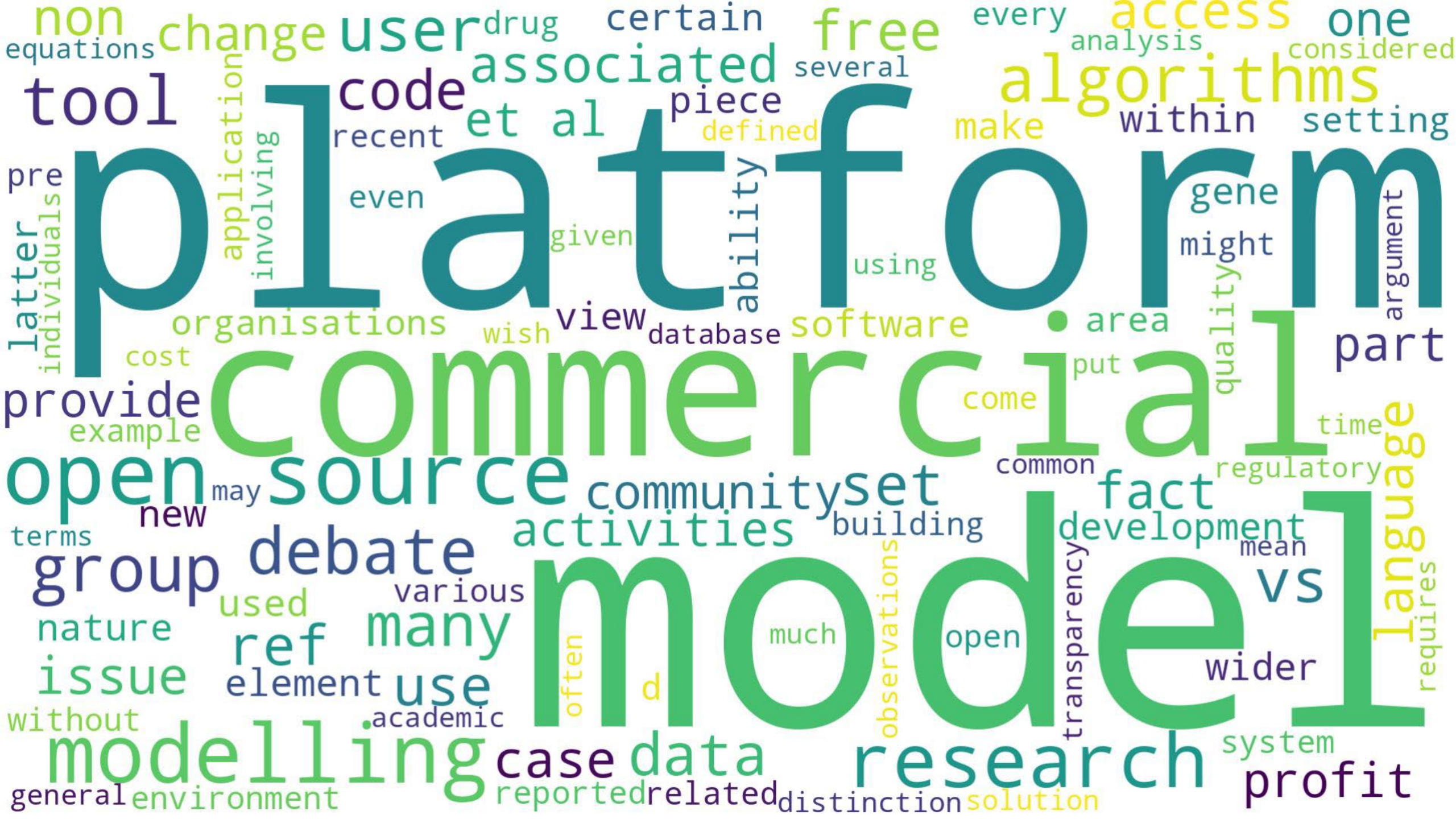
"Unsecure"

Hence

"Vulnerable"

to

"Adulteration"


platform
commercial
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et al
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make
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Pharmaceutical Research
https://doi.org/10.1007/s11095-022-03250-w

2022 - 39(8):1733-1748

Check for updates

WHITE PAPER

Quality Assurance of PBPK Modeling Platforms and Guidance on Building, Evaluating, Verifying and Applying PBPK Models Prudently under the Umbrella of Qualification: Why, When, What, How and By Whom?

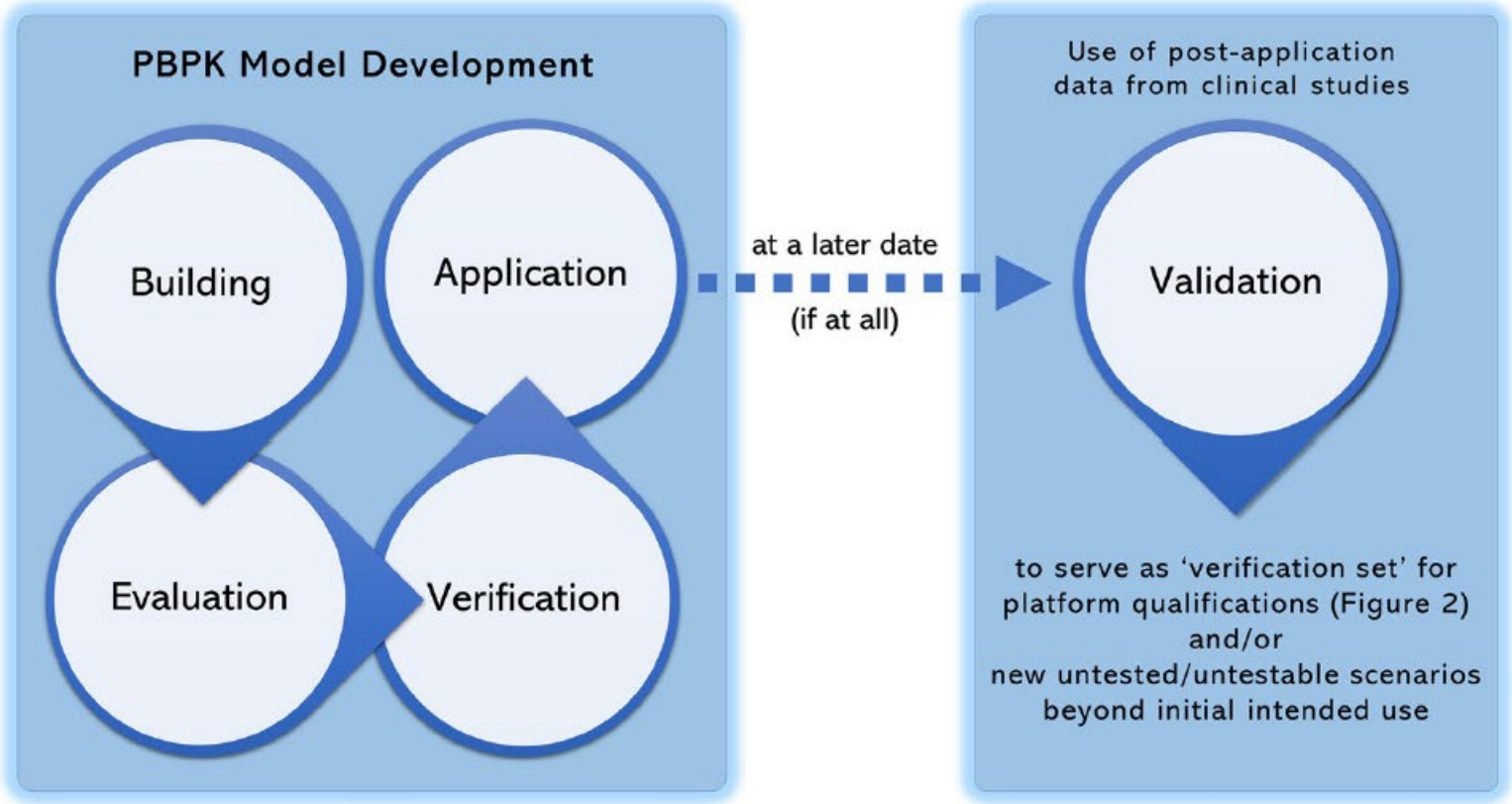
Sebastian Frechen, &
Amin Rostami-Hodjegan

Evaluation of Submissions

Distinguishing between:

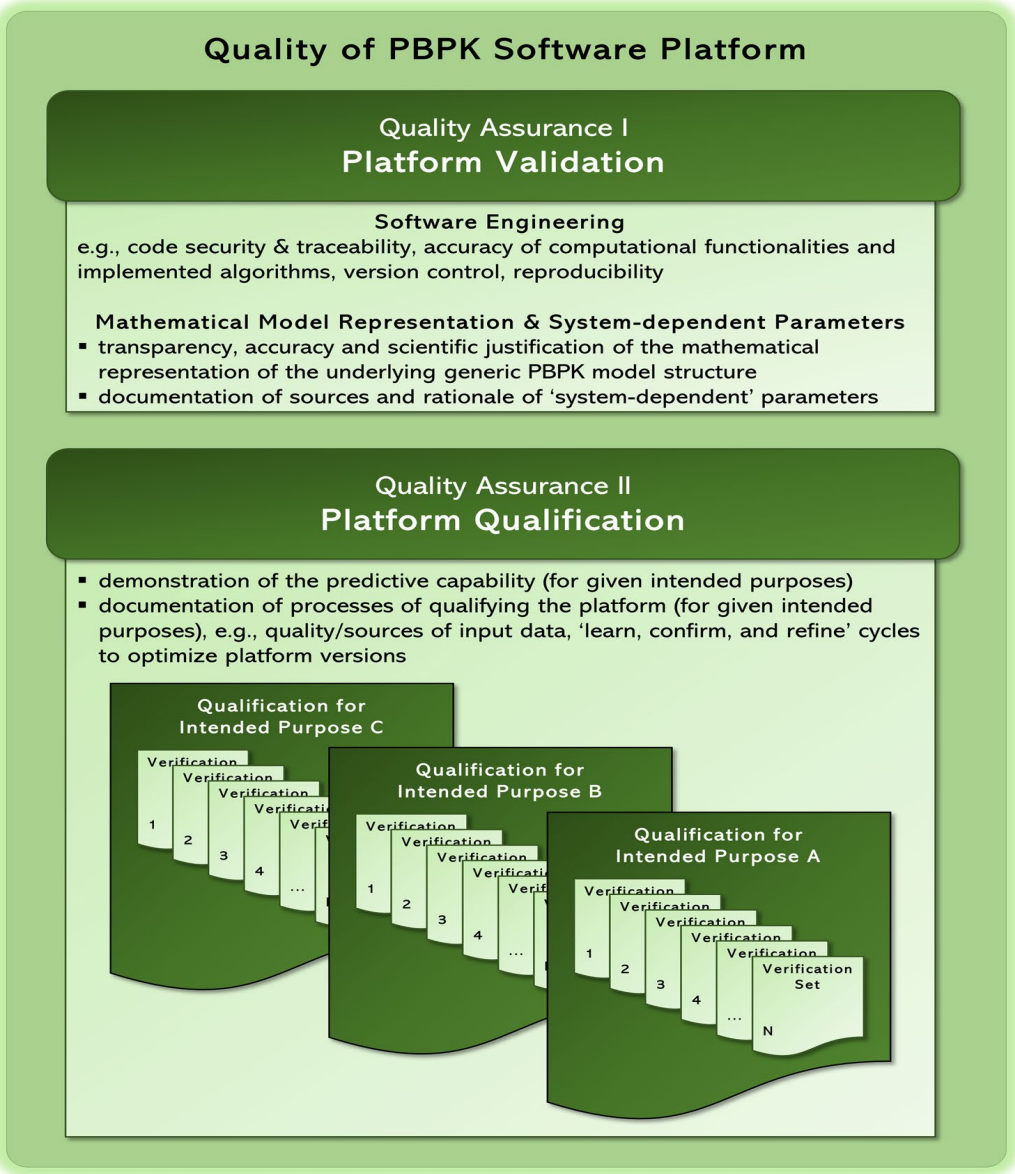
- **Validation**
- **Verification**
- **Qualification**

- **Model Credibility?**

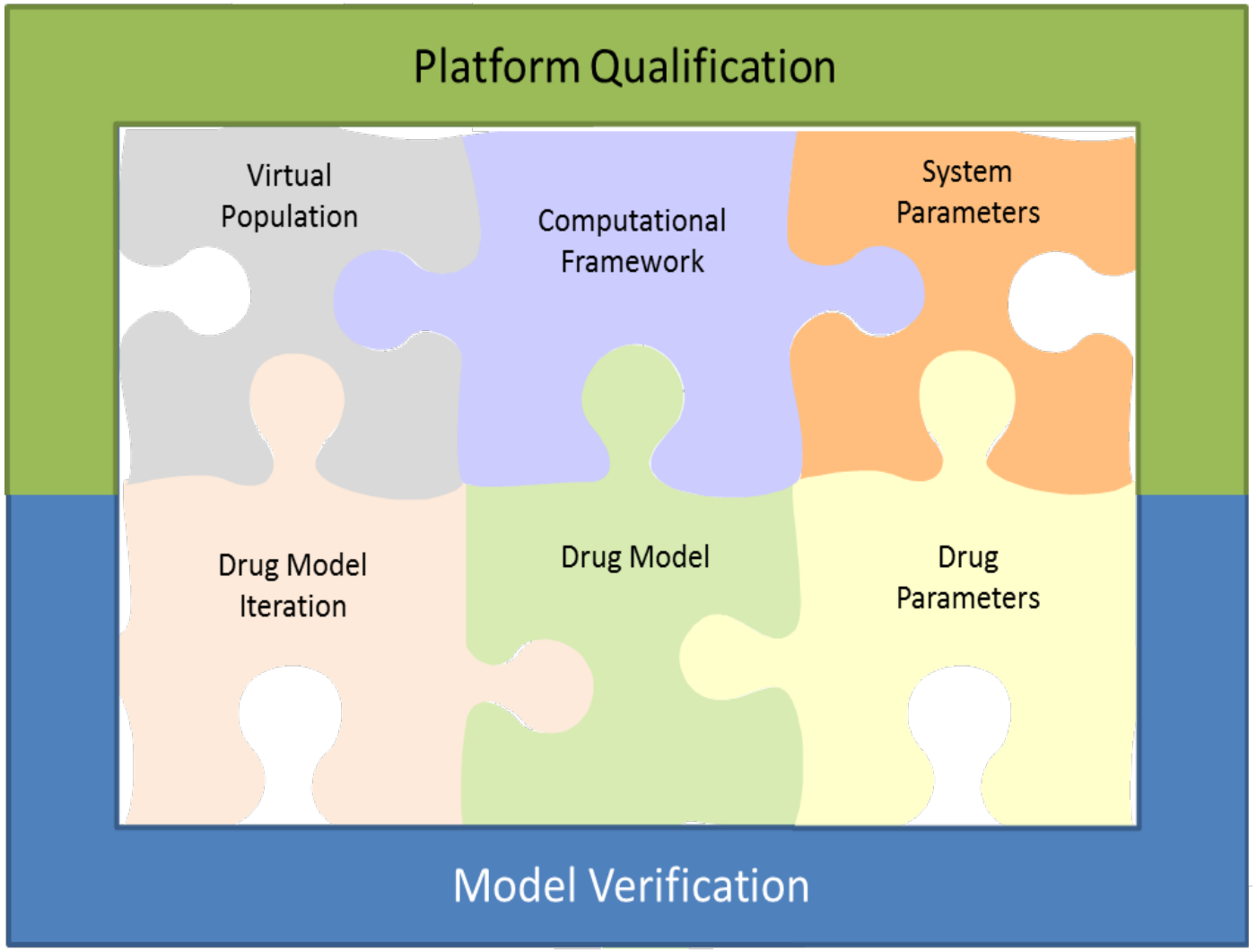


Platform Validation (Code) vs Qualification (Certain Area of Application)

Frechen, & Rostami-Hodjegan, *Pharm Res* 2022



Assessing Platform *vs* Model



Shebley et al 2018 *Clin Pharm Ther* 104 (1): 88-110

Biopharmaceutics & Drug Disposition

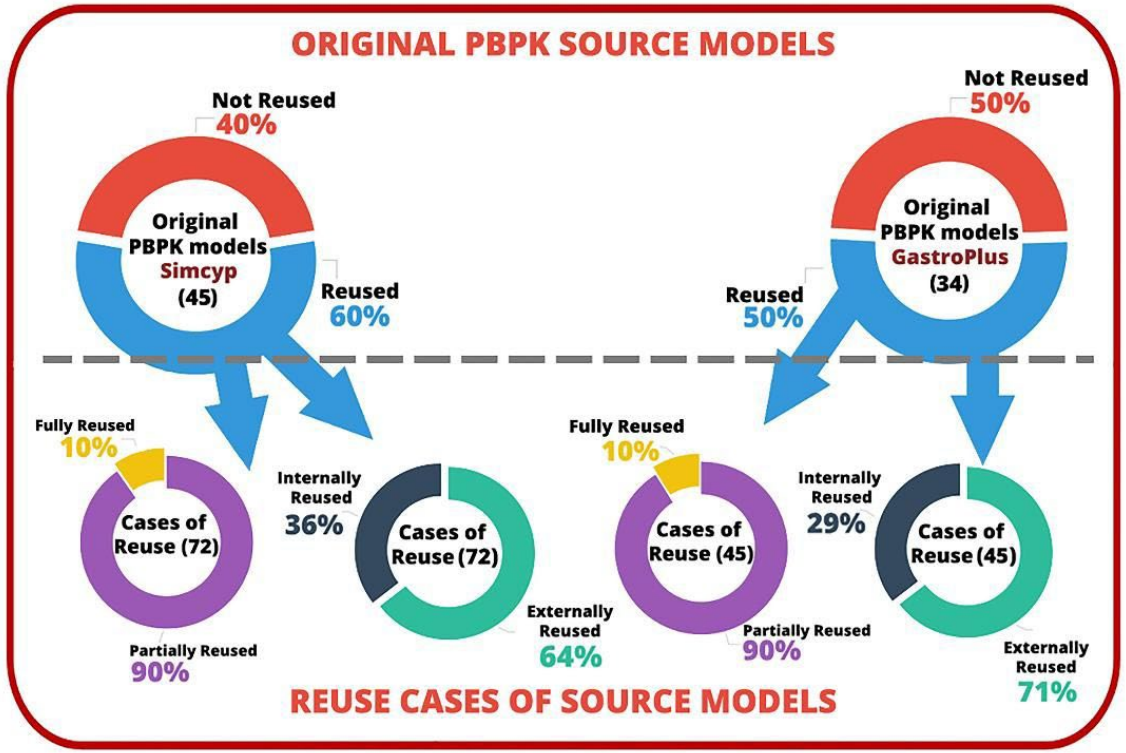
Biopharm Drug Dispos 2023 – UNDER REVIEW

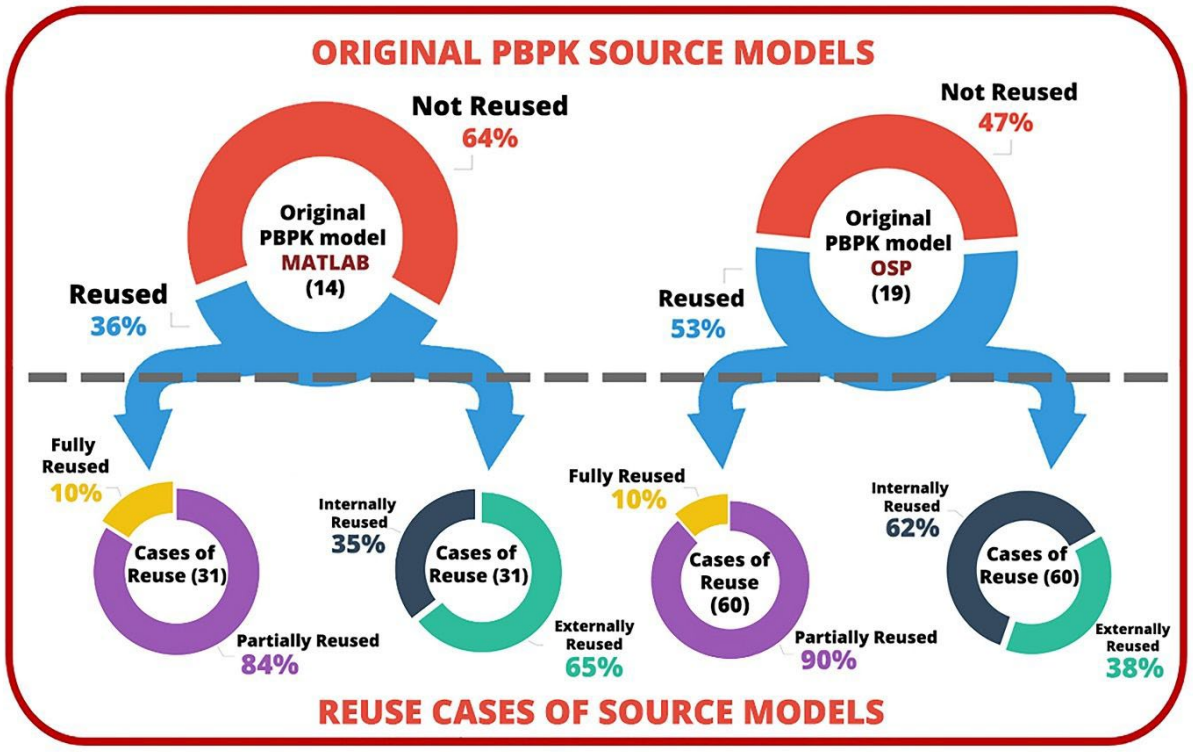
Philosophical Stop No 4

In-Depth Analysis of Patterns in Selection of Different Physiologically-Based Pharmacokinetic Modeling Tools:

Part I - Applications and Rationale Behind the Use of Open Source-Code Software

Part II - Assessment of Model Reusability and Comparison Between Open and Non-Open Source-Code Software





Reusability Concept for Models (rather than Software)

A computational model is considered **entirely reusable** if it may be **utilised** as a simulation component **within other mathematical models**, with its physical scope being the sole constraint

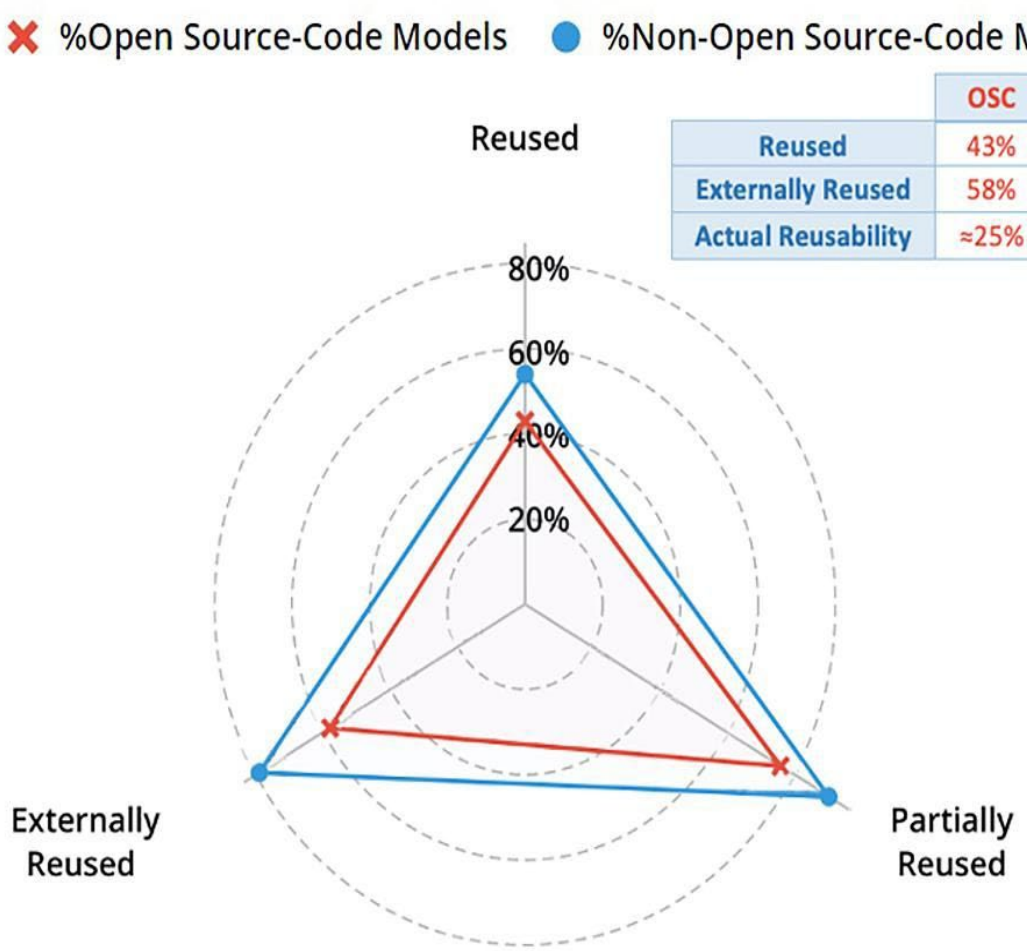
Rodrigues Matos T, *et al.* (2013) On a reusable and multilevel methodology for modeling and simulation of pharmacokinetic-physiological systems: a preliminary study. *Comput Biol Med.* 43(10):1512-22.

Definitions - Current Analysis by the University of Manchester for PBPK Models Reusability

Term	Definition
Reusability	The reutilisation of (I) the model in its entirety, (II) the systems components, (III) the drug-dependent components, (IV) the modelling strategy, or (V) Leveraging the aforementioned
Partial Reusability	(II), (III), (IV) or (V) above
Full Reusability	(I) above
External Reusability	Reusability by researchers outside the organisations affiliated to original model development
Internal Reusability	Reusability of involving researchers from the same institution involved in the development of original model

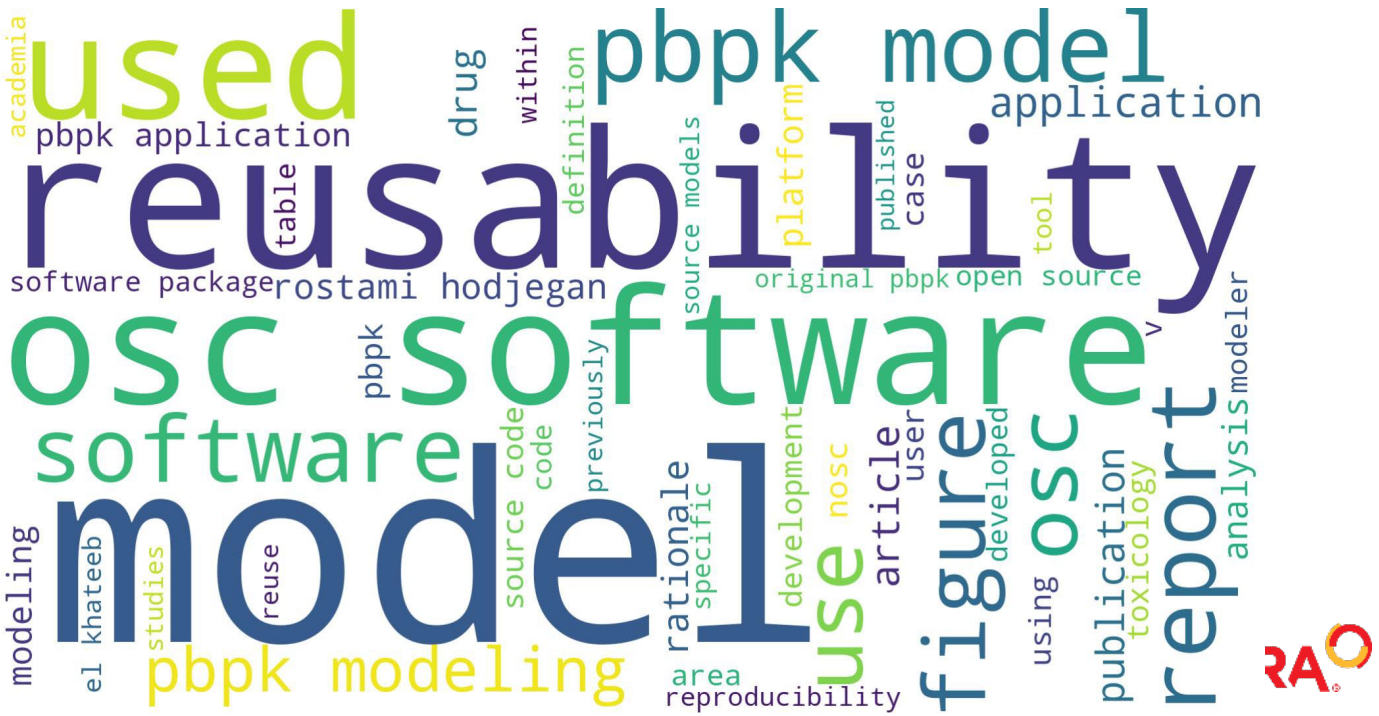
Open Source-Code (24%) << (48%) Non-Open Source-Code

External Reusability:



	OSC	NOSC
Reused	43%	60%
Externally Reused	58%	79%
Actual Reusability	≈25%	≈50%

An Essential Requirement for An Ideal Model Master File



Pharmaceutical Research
https://doi.org/10.1007/s11095-022-03250-w
2022 - 39(8):1733-1748

WHITE PAPER

Quality Assurance of PBPK Modeling Platforms and Guidance on Building, Evaluating, Verifying and Applying PBPK Models Prudently under the Umbrella of Qualification: Why, When, What, How and By Whom?

Unresolved Issues - For Debate & Discussions

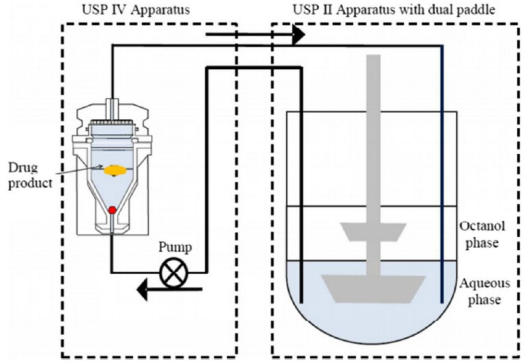
1. Process of Introducing Changes to Models?
2. Frequency of Re-certifying ‘Qualifications’?
3. The Number of Required Verification Cases?
4. Constituents of Transparency (& to whom)?

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

REVIEW ARTICLE

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]



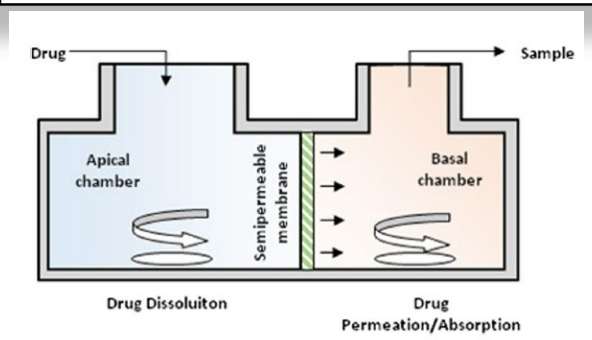
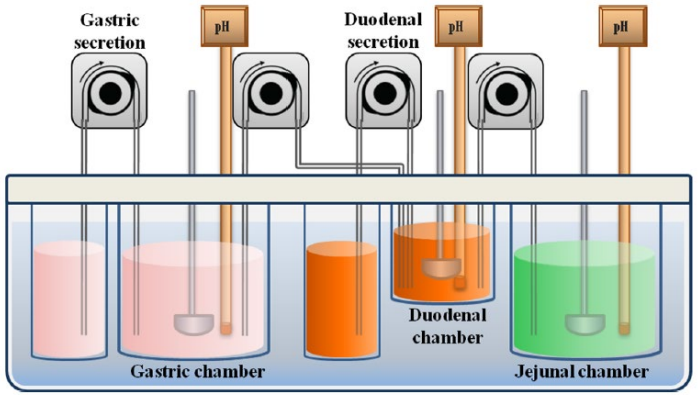


Fig. 1 Schematic of the dissolution/permeation (D/P) system



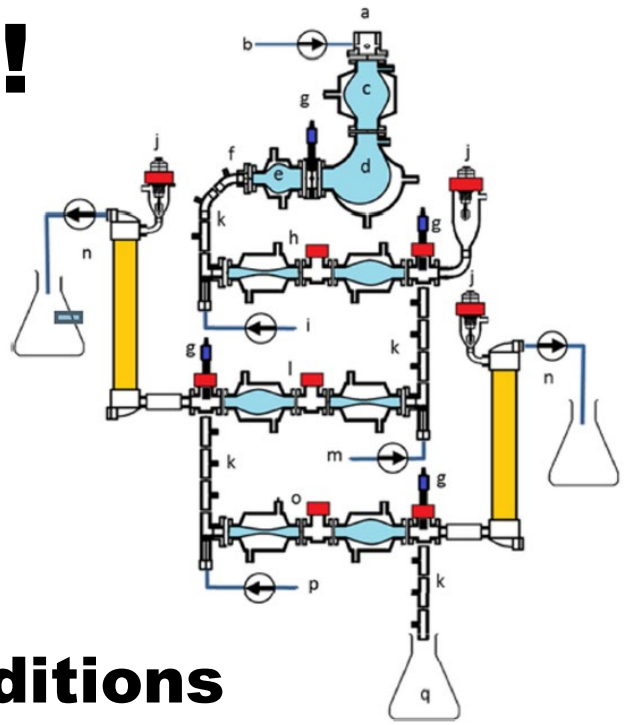
Wrong Philosophy!

There is

NO UNIQUE

‘Predictive Dissolution’

That Caters for ‘All’ Clinical Conditions



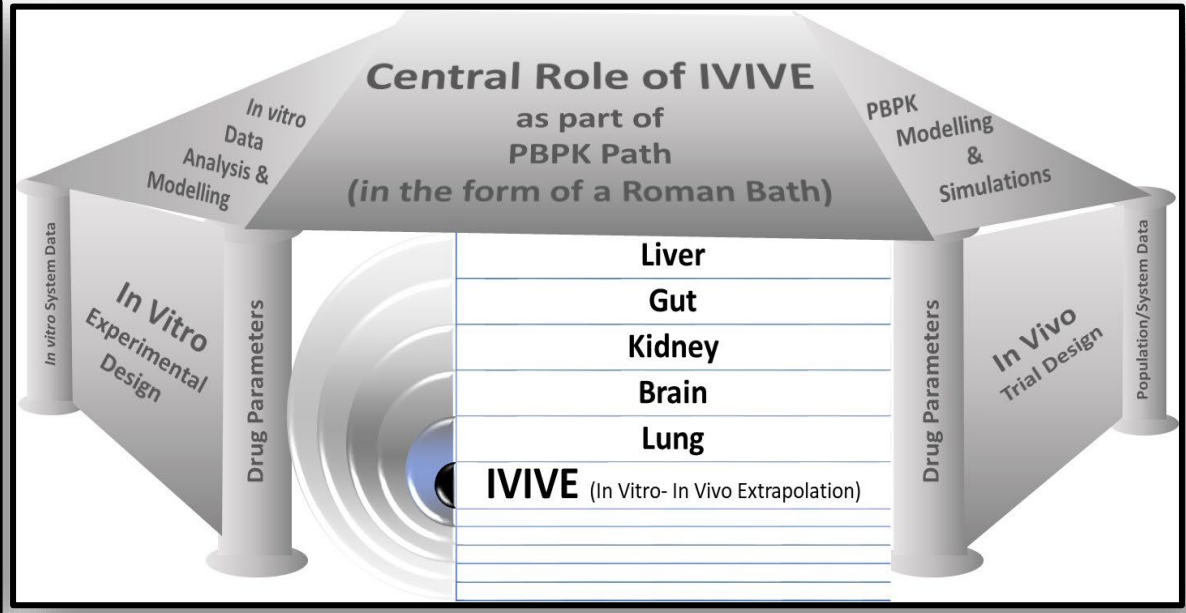
23

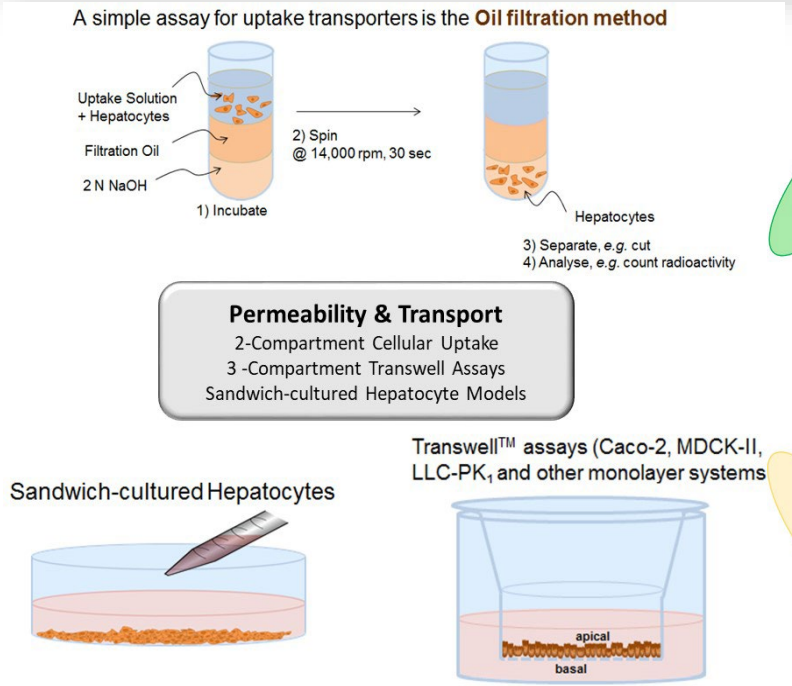
APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC AND PHARMACODYNAMIC (PBPK/PD) MODELING COMPRISING TRANSPORTERS: DELINEATING THE ROLE OF VARIOUS FACTORS IN DRUG DISPOSITION AND TOXICITY

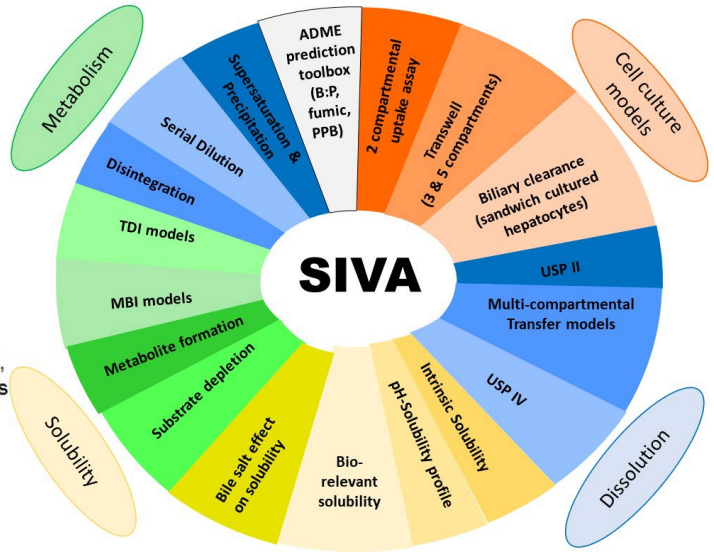
MATTHEW D. HARWOOD[1], AMIN ROSTAMI-HODJEGAN[1,2], AND SIBYLLE NEUHOFF[1]

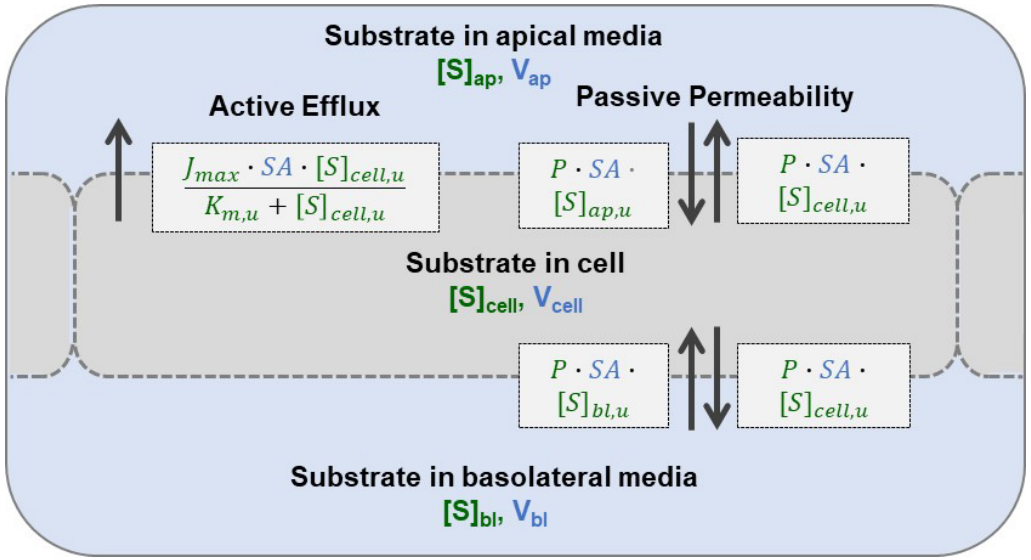
[1] *Simcyp Division, Certara UK Ltd., Sheffield, UK*

[2] *Centre for Applied Pharmacokinetic Research, University of Manchester, Manchester, UK*







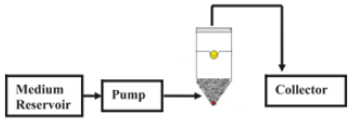


Distinguishing between the Type of Data: '*In Vitro* Set-Dependent' *vs* 'Intrinsic Parameters'

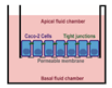
Modeling biopharmaceutic data

Solubility

Dissolution

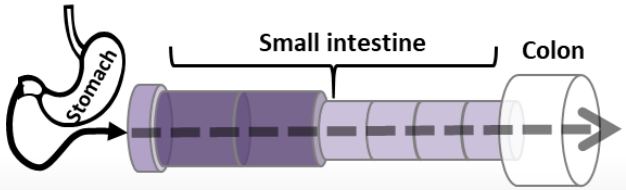


Dissolution

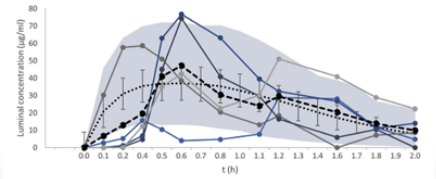


Permeability

Integrating biopharmaceutics with gastrointestinal physiology and variability



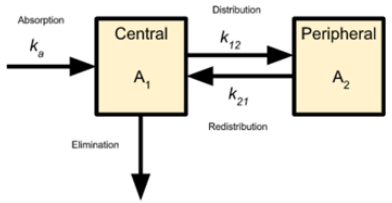
Simulating intraluminal concentrations at individual level



Assessing model performance and credibility at intraluminal level

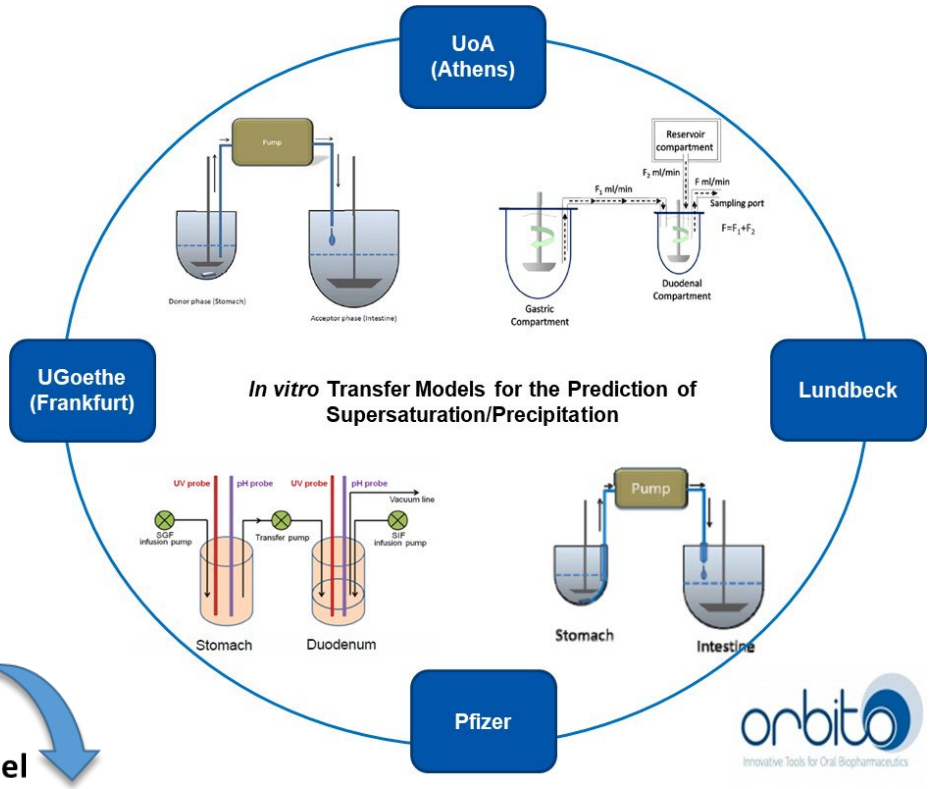
Model refinement

Integrating absorption and disposition models to simulate systemic exposure



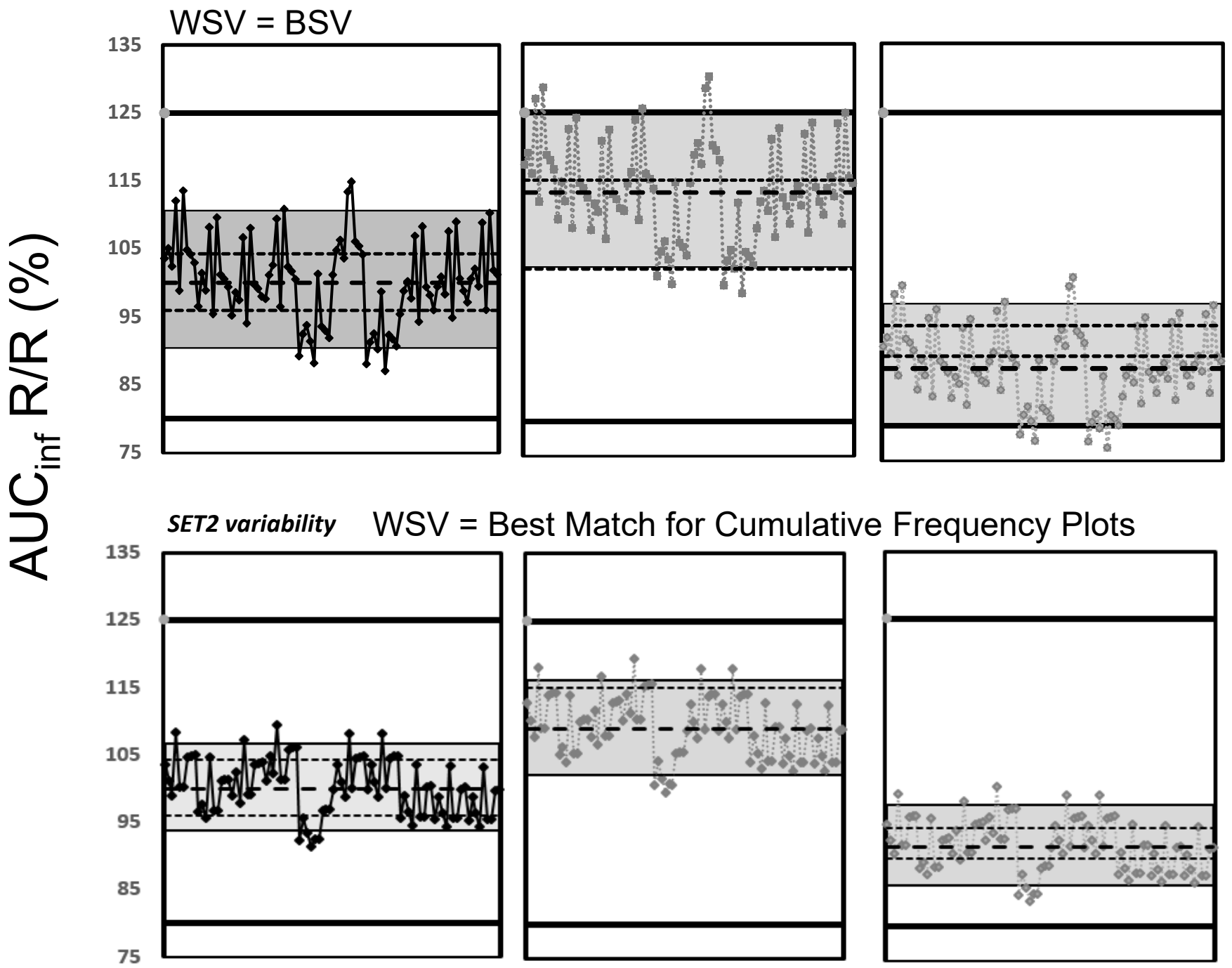
Assessing model performance and credibility at systemic level

Model refinement



orbito
Innovative Tools for Oral Biopharmaceutics

Interplay of Drug (Metabolism/Transport) & Formulation (Disintegration, Dissolution) with System

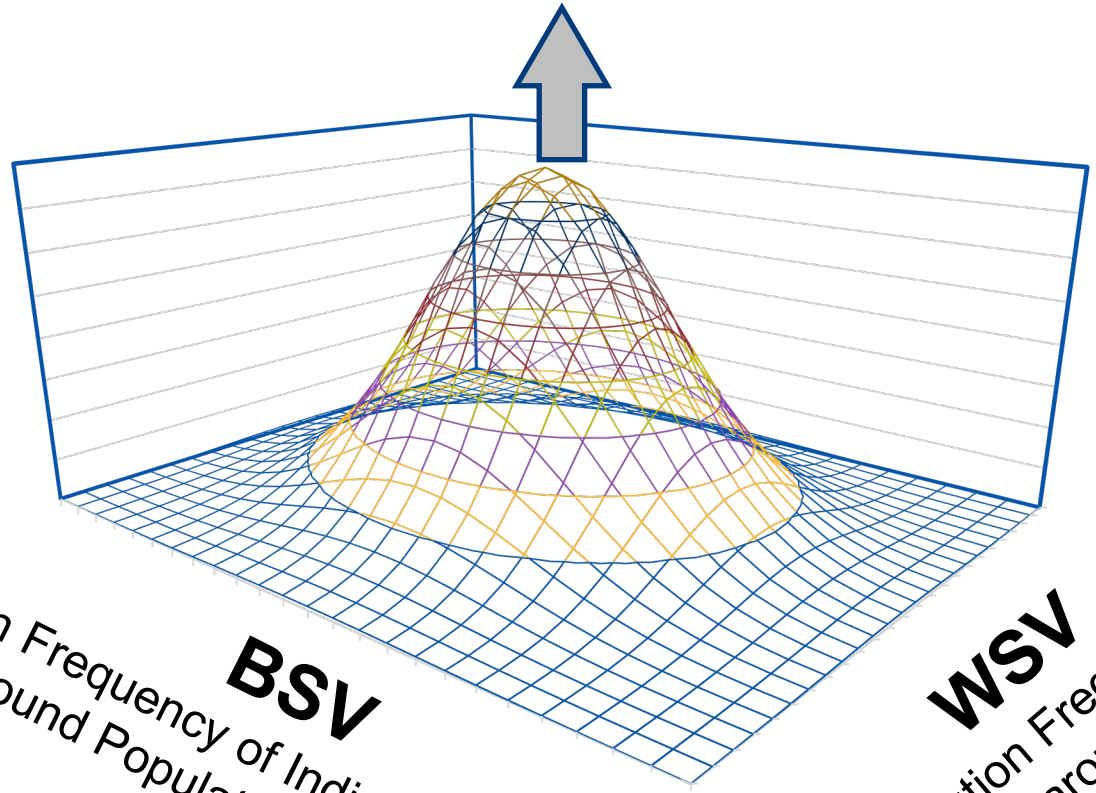


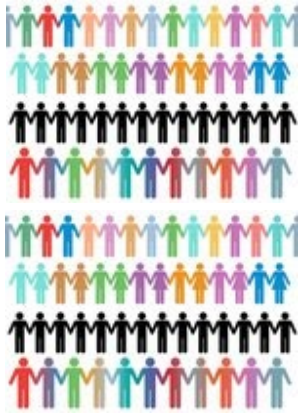
Implications for VBE Studies & Predicting the Likelihood of Passing the Criteria with Given Number of Subjects

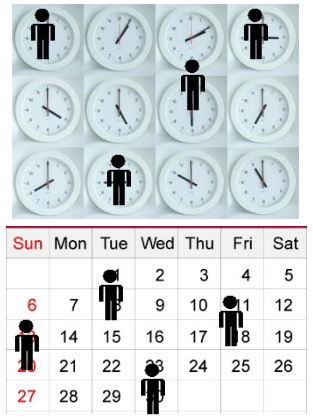
- Likelihood
- BE Interval (80-125%)
- Predicted Outcomes
- Median of VBE's
- Overlay of Clinical Data

Apparent BSV

(Under Single Sampling from Each Individual – as a Hybrid Measure of BSV & WSV)







BSV

Distribution Frequency of Individual Mean Values Around Population Mean Value

WSV

Distribution Frequency of Individual Values around Their Own Mean

True BSV

(Based on Mean Values of Individuals)

WSV

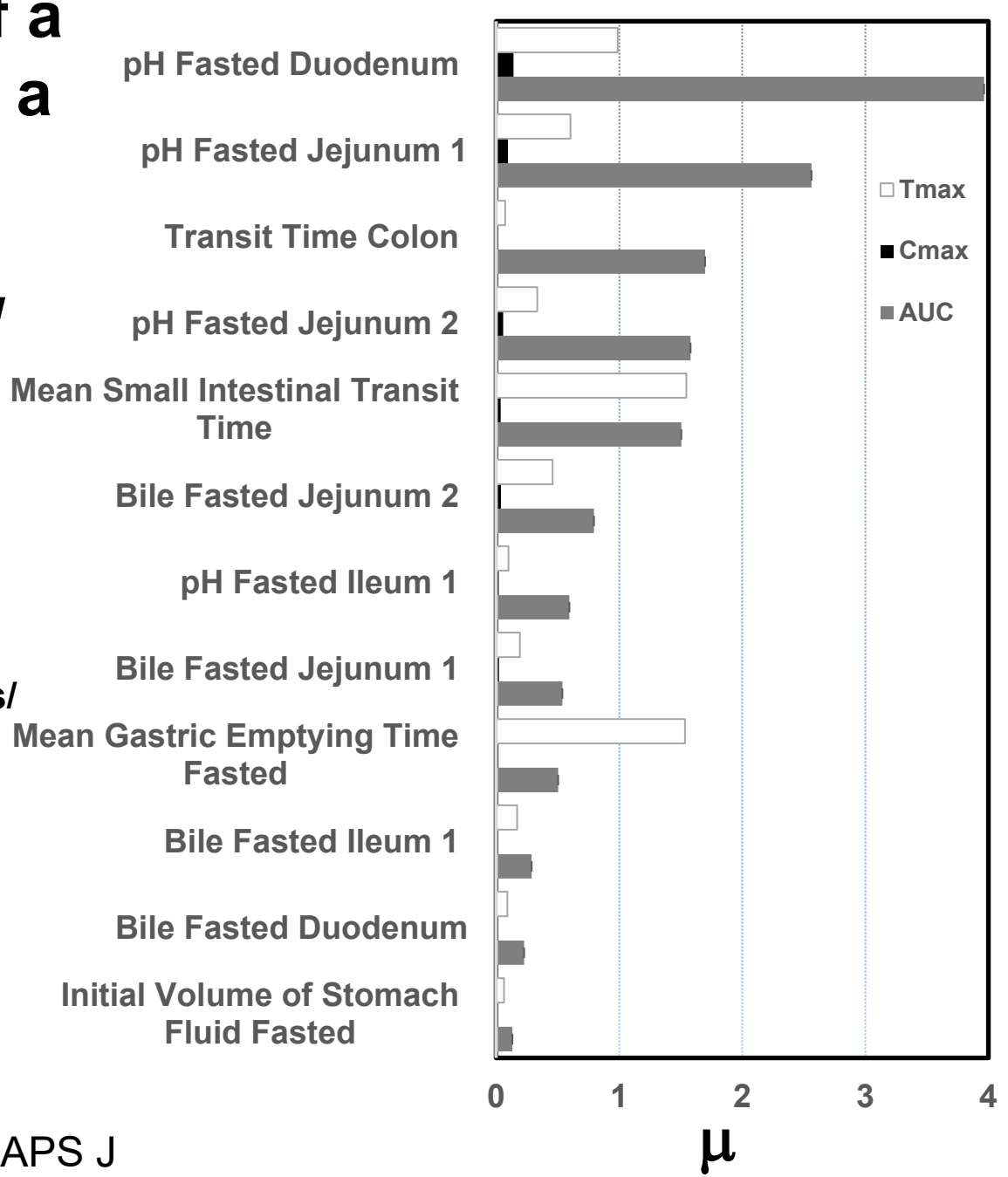
(Under Repeat Sampling from an Individual)

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

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

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

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Relevance of Model Master File

Avoids Starting from Scratch!

Gives Ease of Assessment!

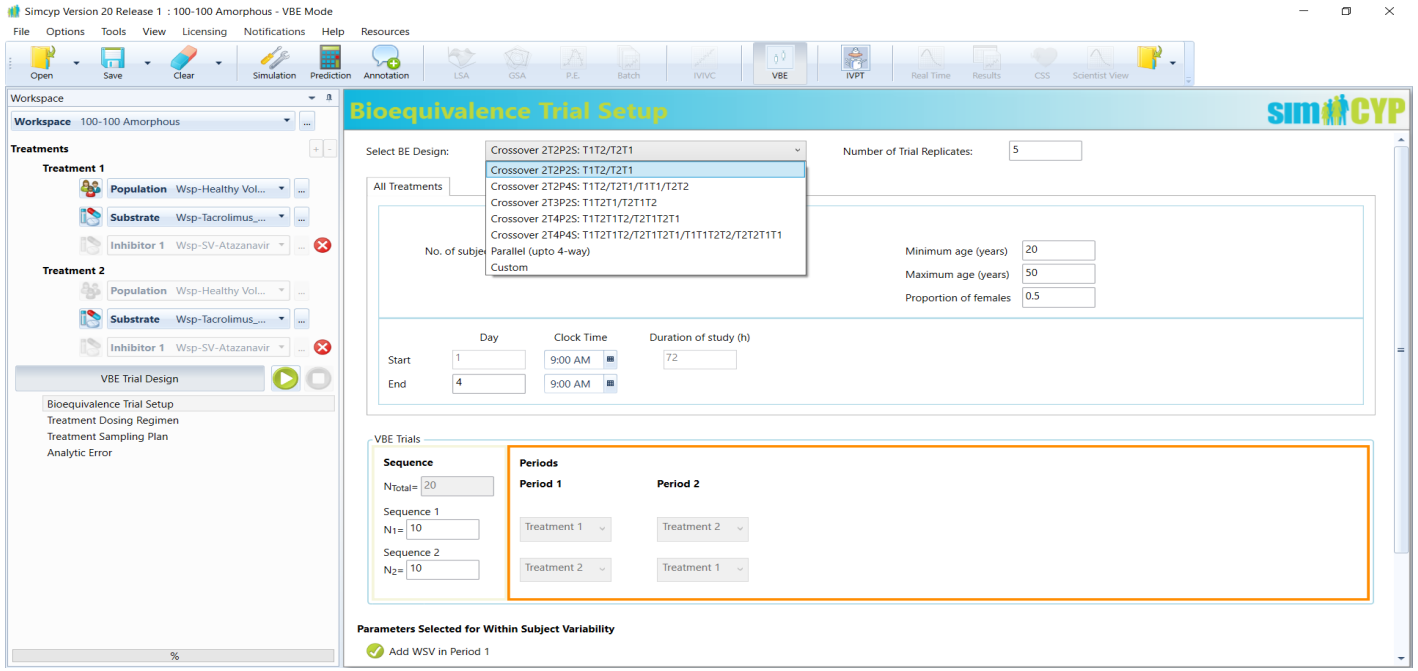
By

Accumulating *CONTINUOUS* Effort on Using Previous Studies on VARIOUS DRUGS/FORMULATIONS and Gaining Insight into DRUG/FORMULATION-INDEPENDENT PARAMETERS

These Can be Incorporated in Any User-Friendly Model Master File Specifically Built

for

VBE



Thanks for Listening

Questions?