MANCHESTER 1824

State of the Art

WHERE WE WERE? WHERE WE ARE NOW? WHERE ARE WE HEADING TOWARDS?

A 3 DECADE TALE OF MODEL-INFORMED DRUG DEVELOPMENT (MIDD) AND ACCOUNT OF PBPK/IVIVE LINK

Amin Rostami

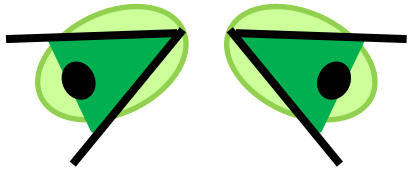
Professor of Systems Pharmacology,
Director of CAPKR
University of Manchester, UK

&

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

Introduction - Horizontal Perspective

Retrospective **Prospective**



Past **Present** **Future**

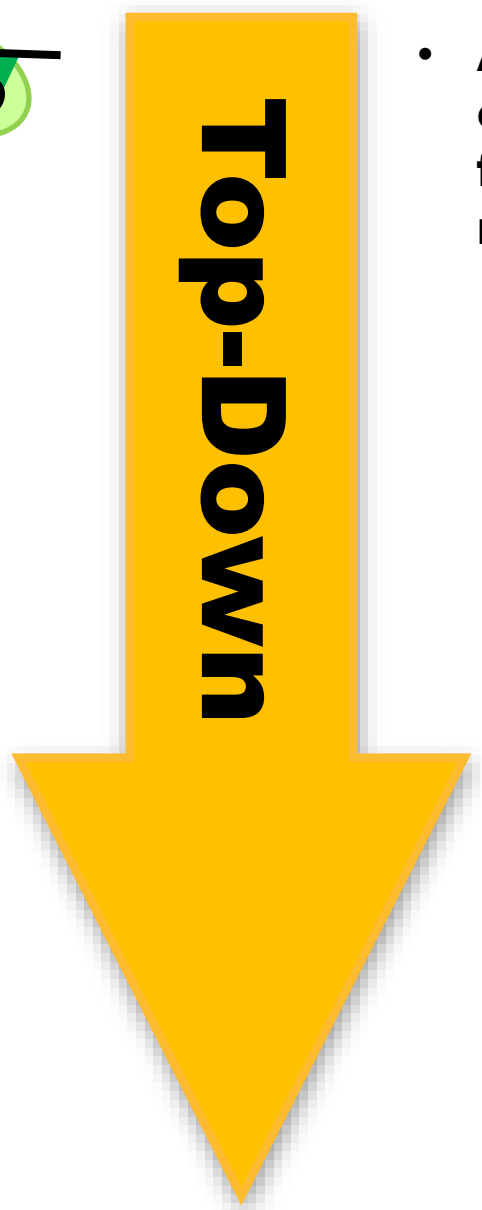
- **Assessing performance**
- **Defining data gaps**
- **Finding linkage**
- **Integrating information**

- **Assessing long term needs**
- **Evaluating required changes**
- **Defining educational gaps**
- **Verifying performance**

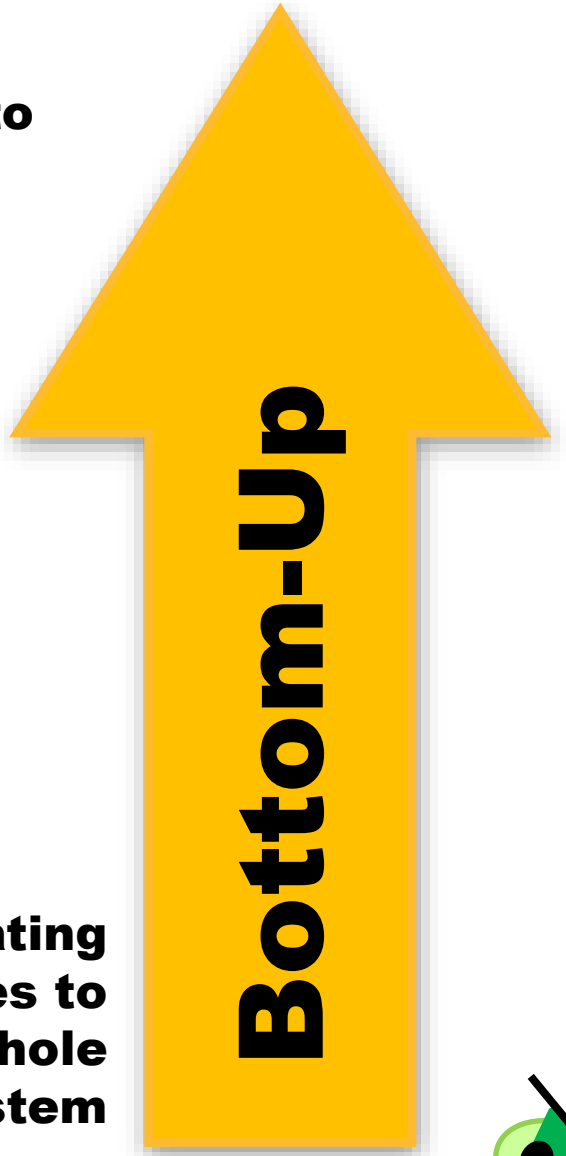
Recommended Reading:

- Rostami-Hodjegan, A. (2024) Conducting Clinical Trials in the Parallel Virtual Universe. *J for Clin Trials 16 (1)*
- Rostami-Hodjegan, A., Darwich, A.S. & Leinfuss, E (2017, December). PBPK Modeling and Simulation: Yesterday's Scientific Endeavor Is Today's Regulatory Necessity. *AAPS Newsmagazine*
- Rowland, M., Lesko, L. & Rostami-Hodjegan, (2015) A. Physiologically based pharmacokinetics is impacting drug development and regulatory decision making. *CPT: pharmacomet. syst. pharmacol* 4, 313-315

Introduction - Vertical Perspective



- **Assessing observed data to find trends and relationships**



- **Integrating discrete pieces to build a whole system**

Recommended Reading:

- Tsamandouras, N., Rostami-Hodjegan, A. & Aarons, L. Combining the "bottom-up" and "top-down" approaches in pharmacokinetic modelling: Fitting PBPK models to observed clinical data. *Br J Clin Pharmacol* **79**, 48-55 (2015).
- Darwich, A.S., Polasek, T.M., Aronson, J.K., Ogungbenro, K., Wright, D. F. B., Achour, B., Reny, J-L., Daali, Y., Eiermann, B., Cook, J., Lesko, L., McLachlan & Rostami-Hodjegan, A. Model-informed Drug Dosing: Background, Requirements, Validation, Implementation and Forward Trajectory of Individualizing Drug Therapy. *Annu Rev Pharmacol Toxicol,* **61**, 225-245 (2021).

University of Manchester: A Global Player

CAPKR

Research Landscape of Physiologically Based Pharmacokinetic Model Utilization in Different Fields: A Bibliometric Analysis (1999–2023)

Xin Wang[1] · Jiangfan Wu[2] · Hongjiang Ye[3] · Xiaofang Zhao[2,4] · Shenyin Zhu[1]

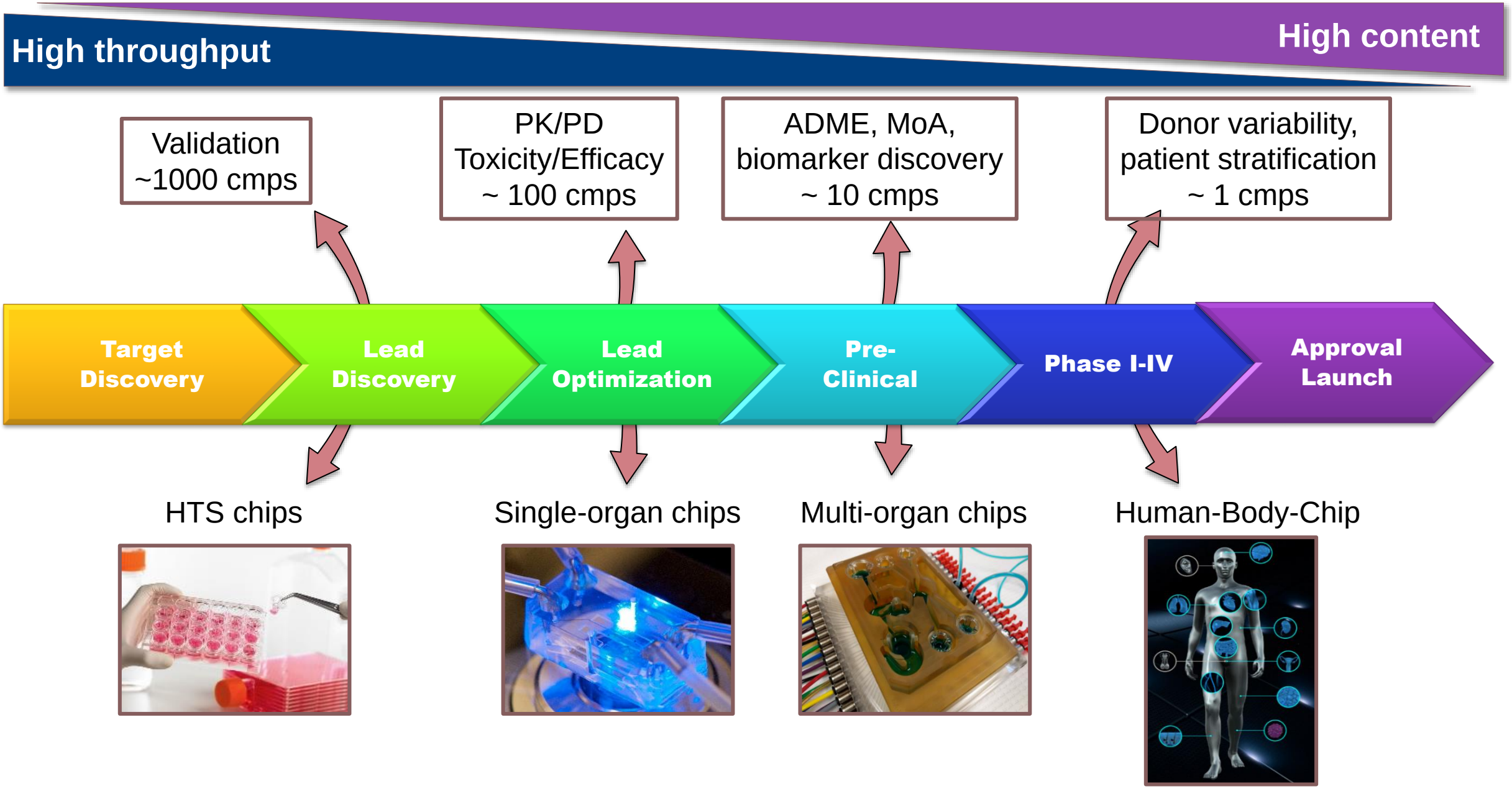
PBPK Universe:

Pharmaceutical Science **Environmental Tox**

Centre for Applied Pharmacokinetics Research

- *TRANSLATIONAL MODELLING*
- PRE-COMPETITIVE *RESEARCH*
- *PRO-ACTIVE* PPLICATIONS
- SCIENTIFIC *LEADERSHIP*

Organ-on-Chip (MPS): Vary Across Pharma and Regulatory Agencies



PBPK/IVIVE Linked Models

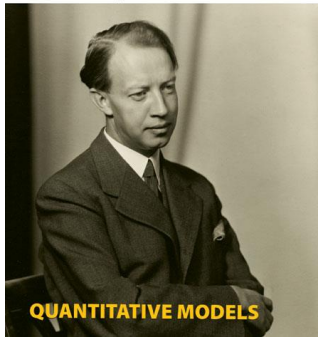
STATE OF THE ART

nature publishing gr

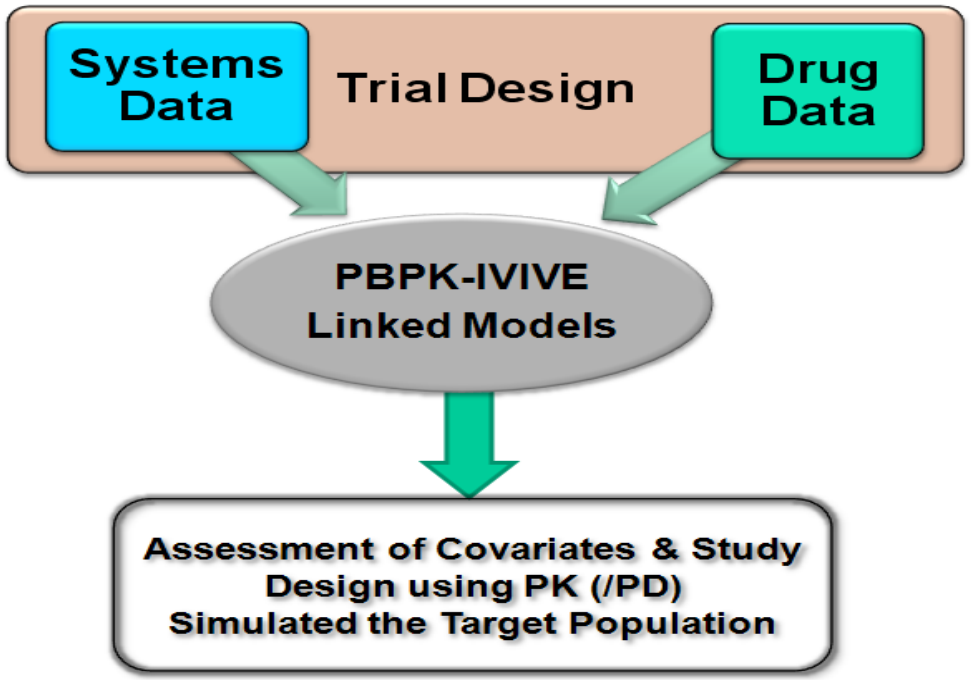
Clinical Pharmacology & Therapeutics

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

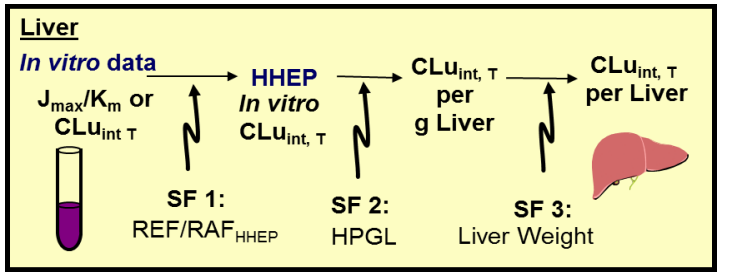


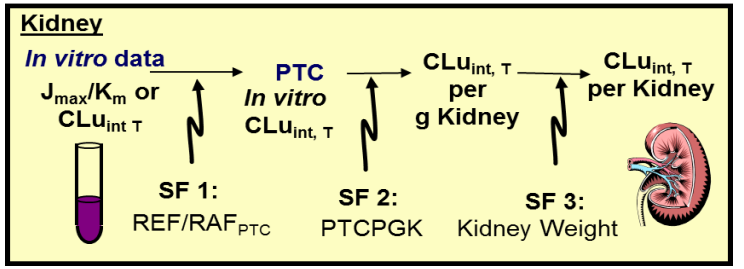
Associated IT Elements

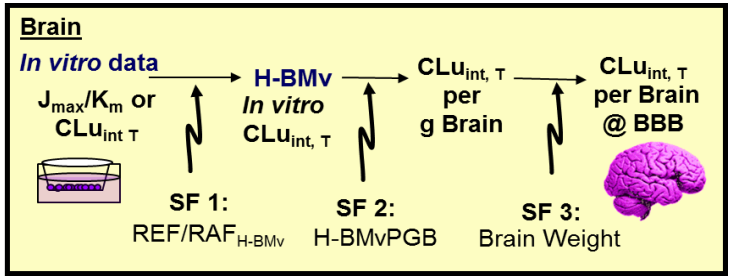
Input Data:
- Population Library
- Compound File
- Project (Workspace)

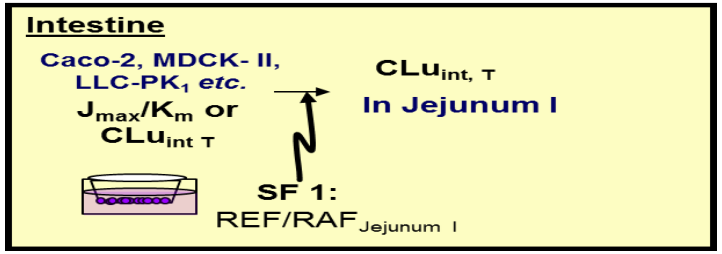
Integrated Models
- Simulation Tool
- Simulation Environment

Output
- Raw Output Data
- Output Environment
- Data Analysis

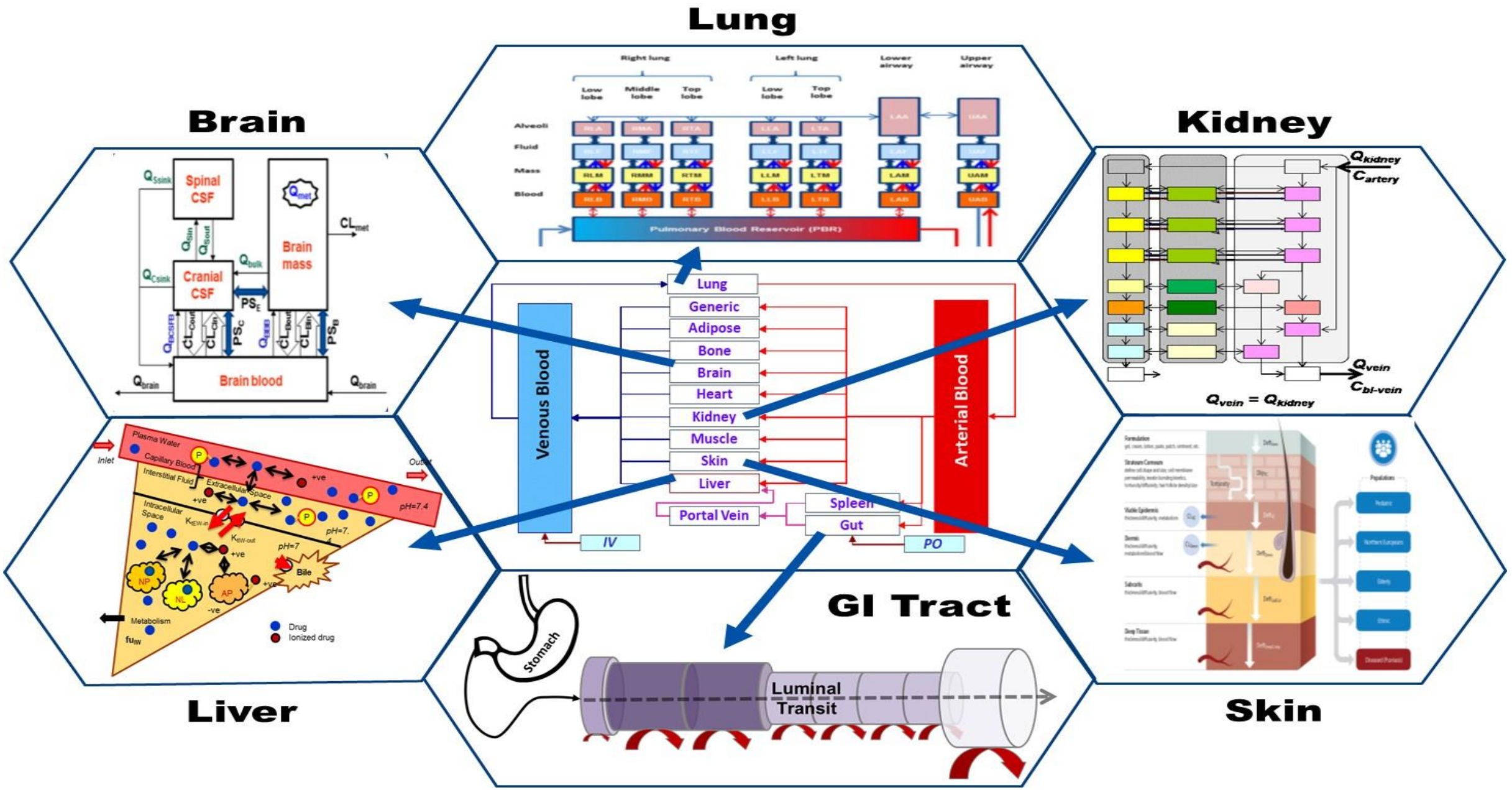








No Longer just Focusing on Systemic Circulation



Filling the Gaps: LCMS/MS Proteomics

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
https://doi.org/10.1080/17425255.2018.1546288

Taylor & Francis
Taylor & Francis Group

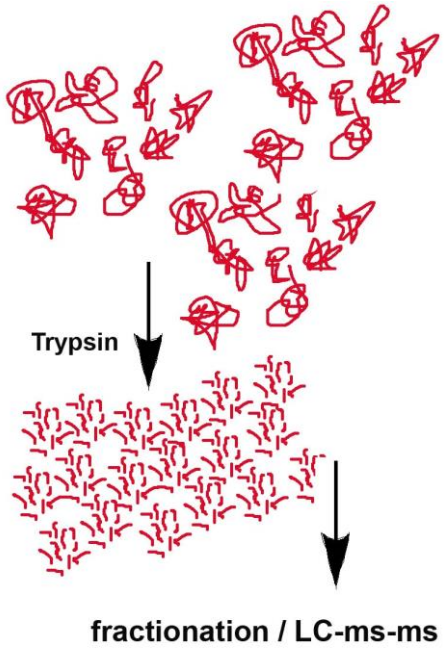
REVIEW

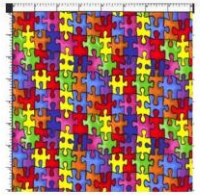
Check for updates

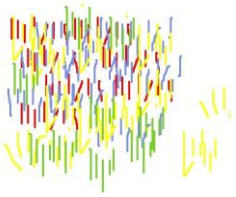
Dose adjustment in orphan disease populations: the quest to fulfill the requirements of physiologically based pharmacokinetics

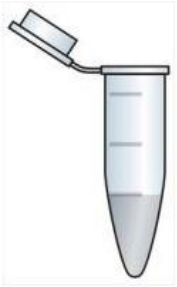
Martyn Howard[a], Jill Barber[a], Naved Alizai[b] and Amin Rostami-Hodjegan[a]

[a]Centre for Applied Pharmacokinetic Research, University of Manchester, Manchester, UK; [b]Leeds General Infirmary, Leeds Children's Hospital, Leeds, UK









Patient Characterisation Methods

Assigning Metabolic/Transport Capacity

Genotyping

Pros: Non-invasive

Limitations: Non-quantitative

Phenotyping cocktails

Pros: Simultaneous assessment of several pathways

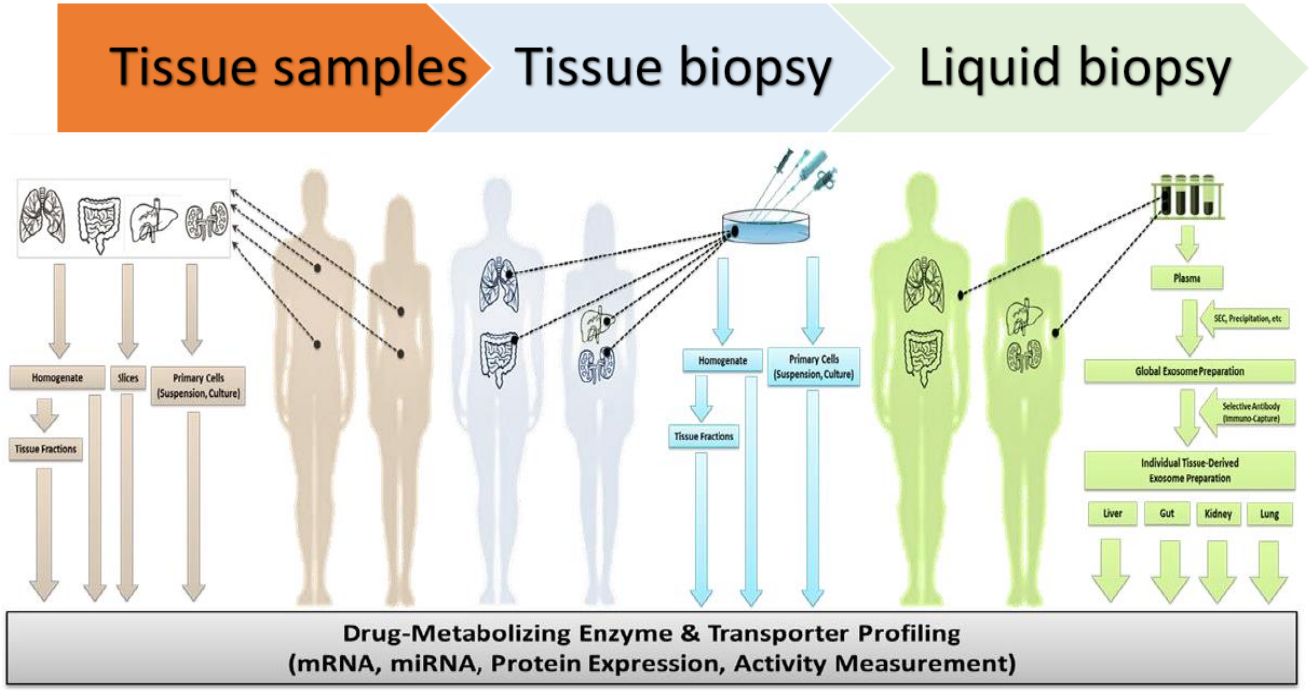
Limitations: Invasive, requires dedicated HPLC for each drug

Endogenous biomarkers

Pros: Non-invasive

Limitations: Limited number; lack of specificity

New characterisation methods*



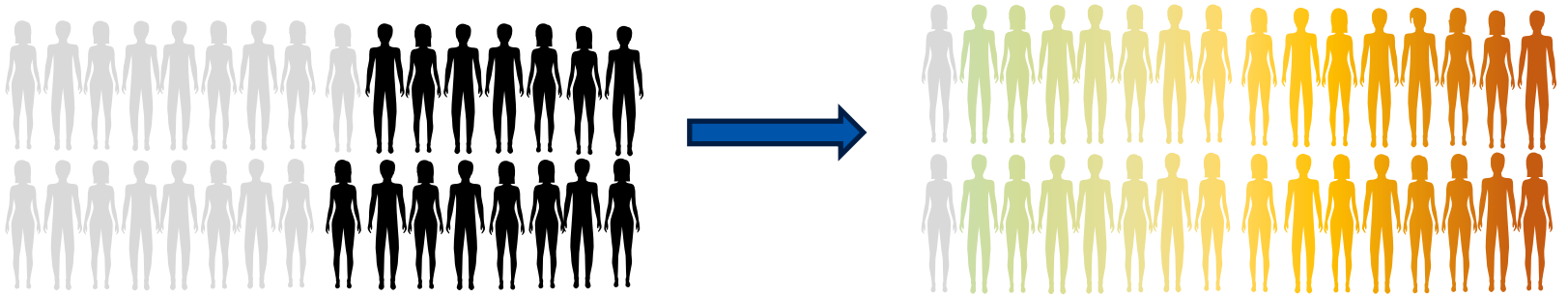
*Expression and/or activity

Rodrigues & Rowland (2020) JPET, 372(3): 308-319

Liquid Biopsy: Quantitative Grade for Virtual Twins

Traditional cancer diagnostic tests

Proposed liquid biopsy use



Is the disease marker expressed?

- No
- Yes

Liquid Biopsy Enables Quantification of the Abundance and Interindividual Variability of Hepatic Enzymes and Transporters

Brahim Achour[1,*], Zubida M. Al-Majdoub[1], Agnieszka Grybos-Gajniak[2], Kristi Lea[3], Peter Kilford[4], Mian Zhang[4], David Knight[5], Jill Barber[1], Jeoffrey Schageman[3] and Amin Rostami-Hodjegan[1,6]

'Liquid Biopsy'

A Game Changer for Handling Variability

HISTORY

GOING BACK OVER 20 YEARS

THE VERY FIRST LOGO OF SIMCYP

SIMCYP Ltd

(No DDI – All about Variability!)

WARNING:

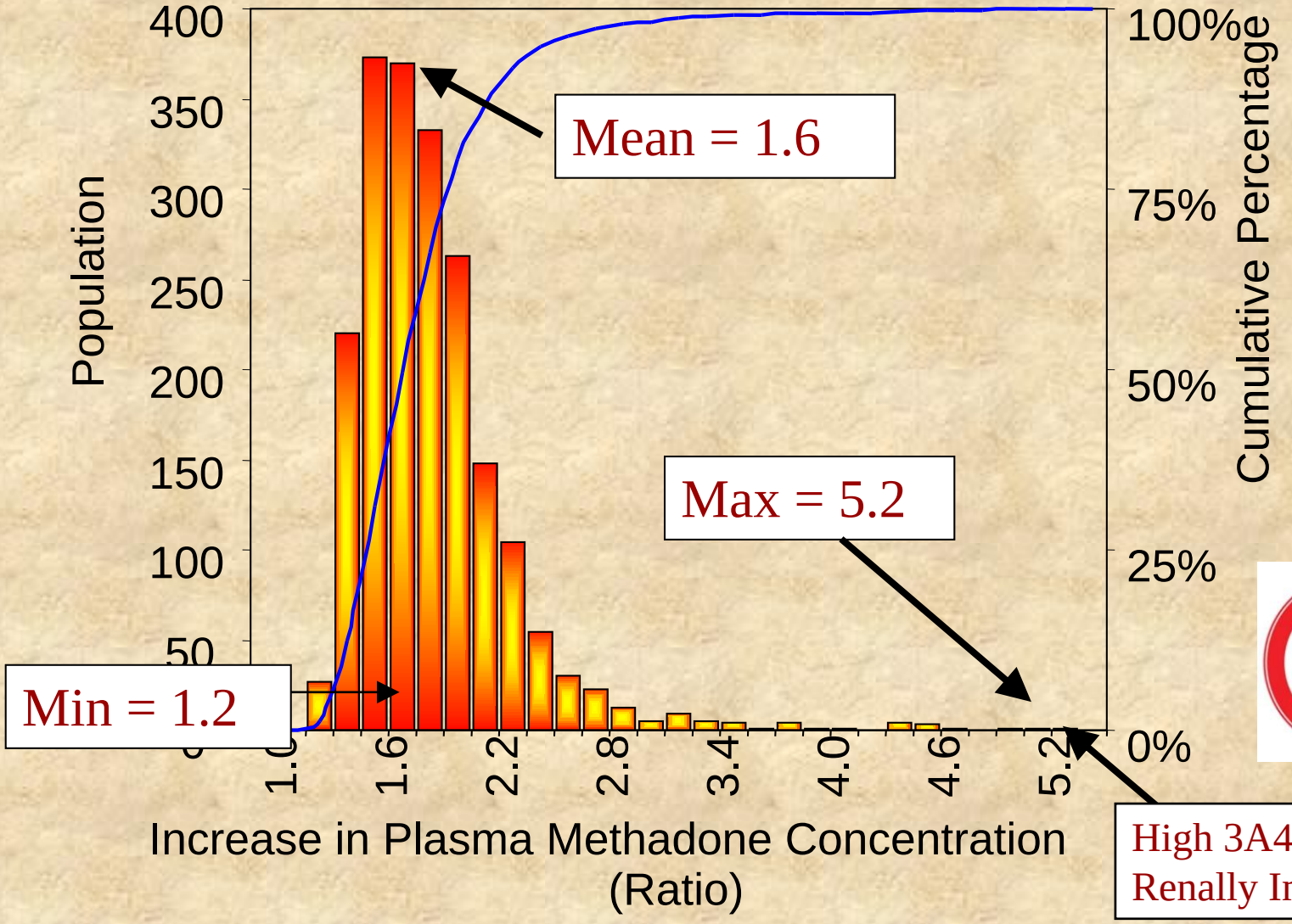
Some **slides in this production are older than 21 years old. Depending on your age, you may find many of the slides something that you had not been exposed to previously. However, they are true documentary reflections on what was considered at the time as attractive!**

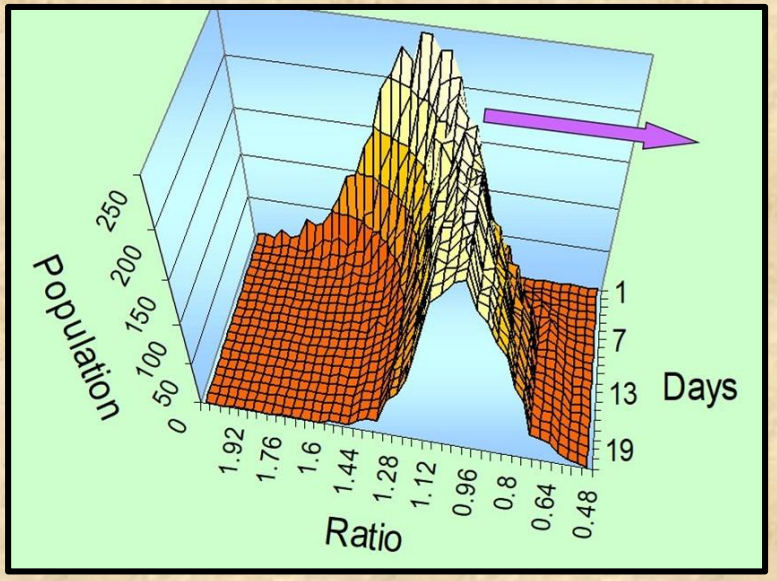
1999: M&S NEEDED A FOOT-HOLD IN DMPK AND VICE VERSA!

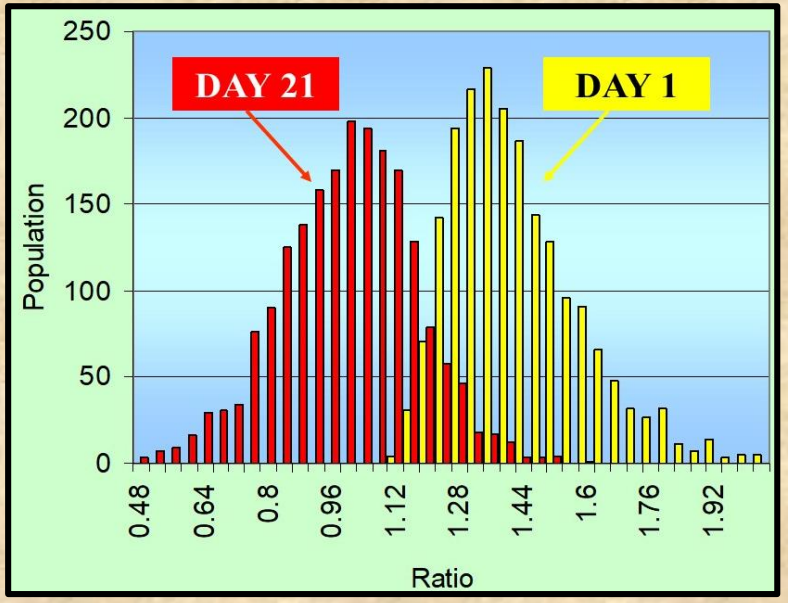
PREDICTING *IN VIVO* INTERACTIONS FROM *IN VITRO* DATA

- *A growing interest.*
- *Previous predictions based on mean data.*
- *Is risk to individuals fully evaluated?*
- *Interpretation of interaction studies should focus not only on mean effect but also the observed and theoretically conceivable extremes (Krayenbühl et al, 1999).*

1999: VISUALISATION OF WHAT PBPK/IVIVE COULD DO WAS ATTRACTIVE







PBPK/IVIVE was Not Restricted to

Fit for Purpose

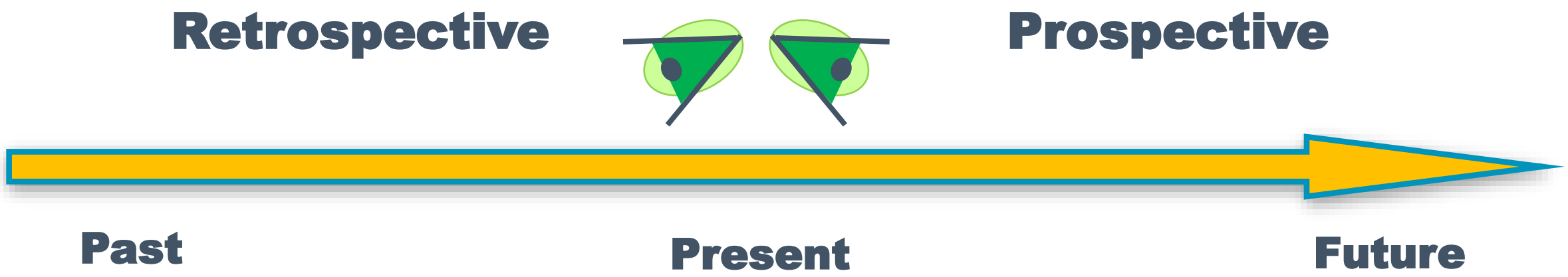
Scenarios

As Applications were

Framed for Future

Queries

Focusing on Lessons Learnt



(1) Simcyp philosophy is mature (>25 years of experience!),

(2) Predicting DDI was the Starting point, and not the end game,

(3) Patient variability was the central piece, and it has remained so until now,

(4) Complexity of human biology and physiology are never ignored,

(5) Greater use of *in vitro* drug data was aligned with improved experiments,

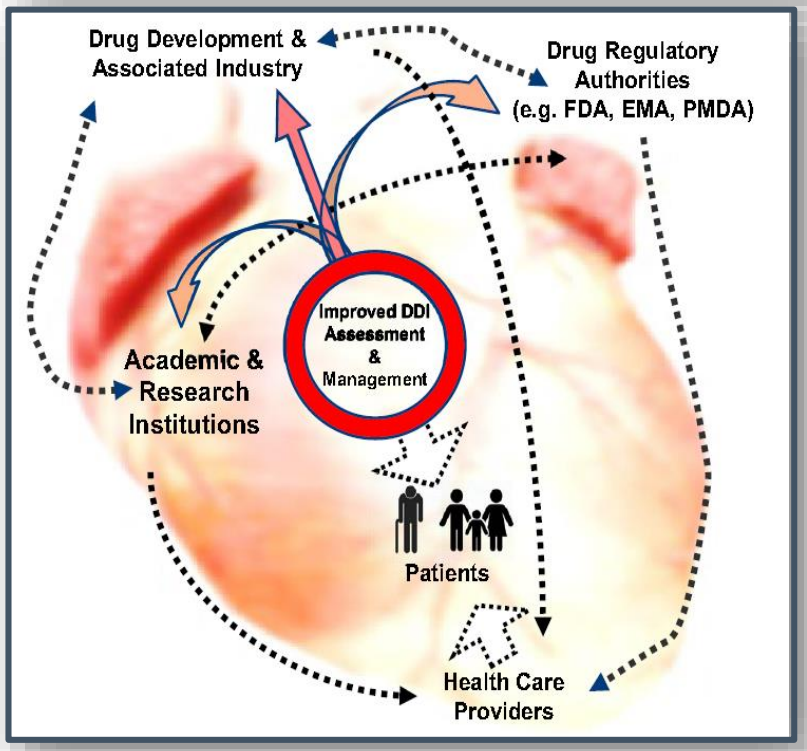
(6) Models/Structure was built for "reusability" rather than one off application.

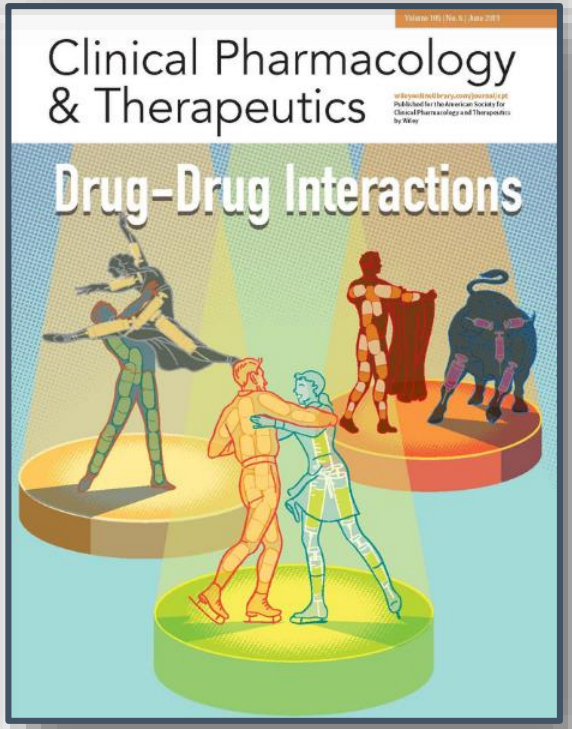
How Did We Do It?

Marathon - **Not A Sprint Event!**
Team-Sport - **Not A Solo Effort!**

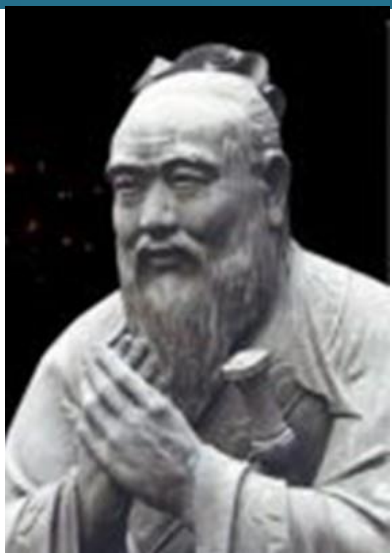
Come Dance With Me: Transformative Changes in the Science and Practice of Drug–Drug Interactions

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





"The man who moves a mountain begins by carrying away small stones"



Confucius

Consortium

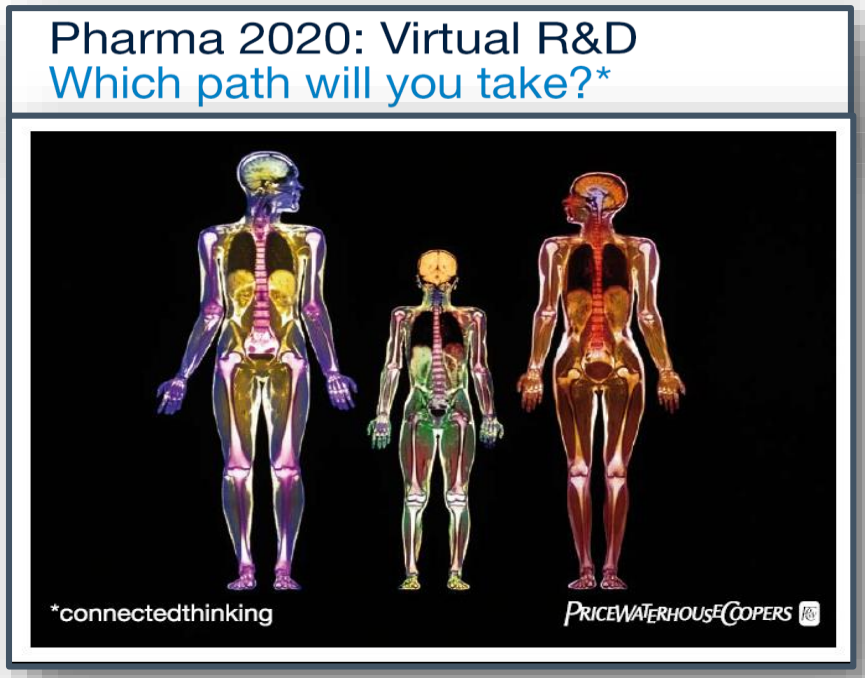
Fostered "Collaborations"

"If you are the smartest person in the room, then you are in the wrong room"

Why Did It Not Go Faster? Predictions for 2020 in 2008!

PricewaterhouseCoopers: Pharma 2020

.... proposes that *new technologies will enable the adoption of* virtual R&D; and by operating in a more connected world, the industry in collaboration with researchers, governments, healthcare payers and providers, can address the changing needs of society more effectively.



Kate Moss June 2008

However, they missed few things:

(1) Requires More Data not Less!

(2) Requires Different Type of Data

(3) Requires Huge Integration Task

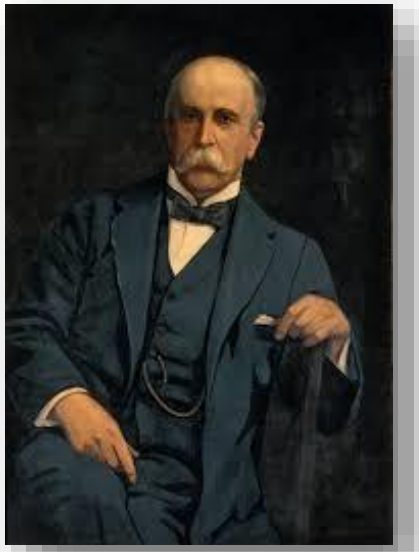
(4) Appropriate Tools Are Essential

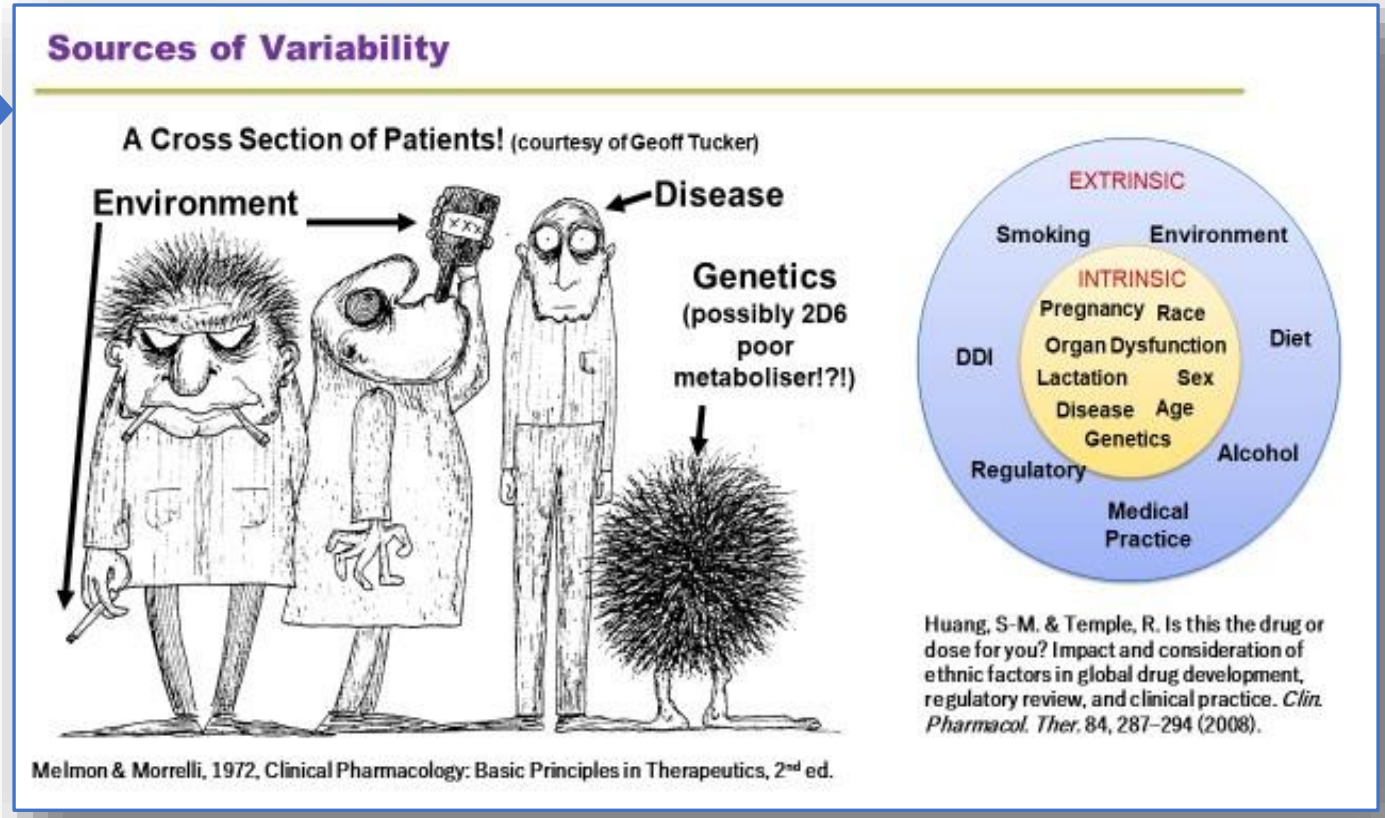
Reality of Special Populations in Clinic

100 Years Old Problem Known within Modern Medicine.

Sir William Osler (1849-1919)

Professor of Medicine Oxford, England



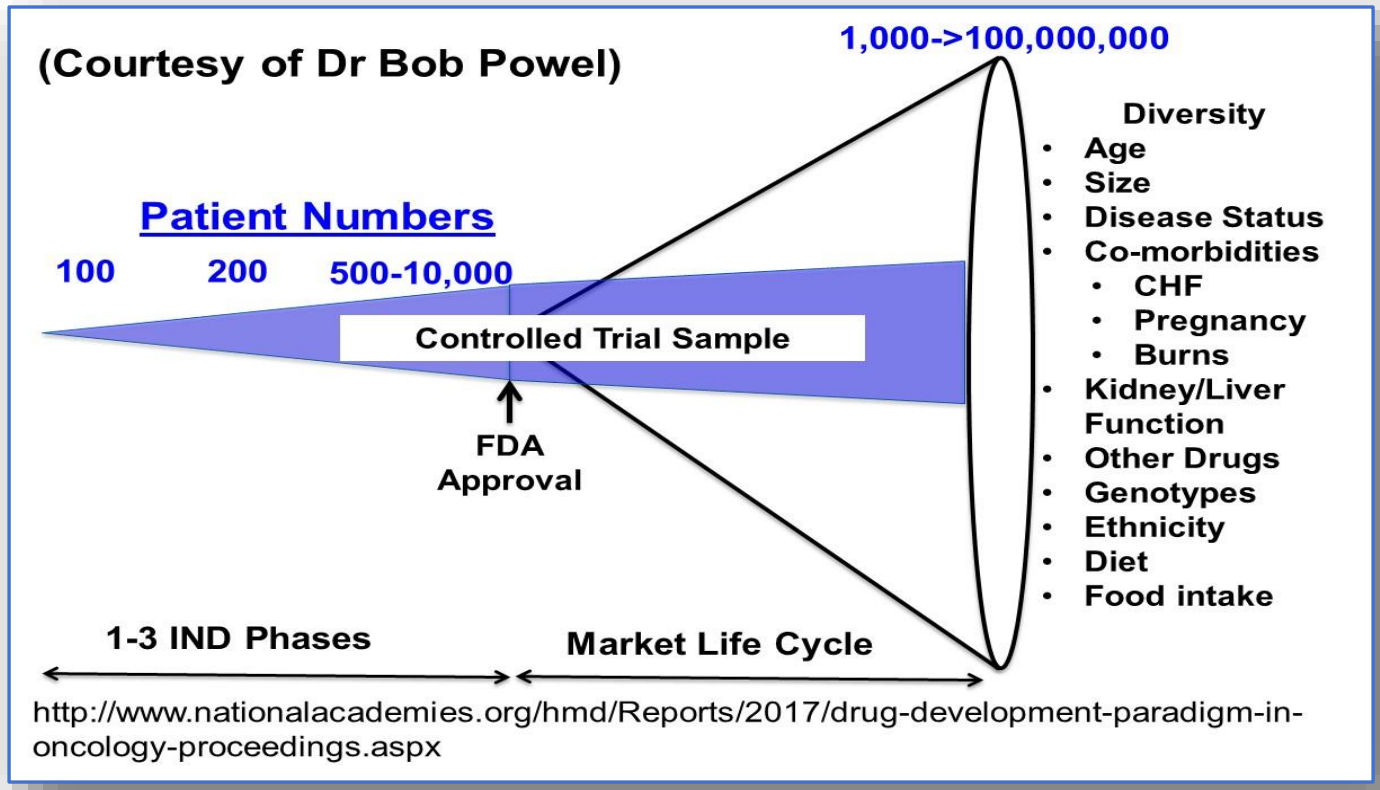


"*Variability is the* law *of life*, and as no two faces are the same, so no two bodies are alike, and no individuals react alike and behave alike under the abnormal conditions which we know as disease"

Issues with Current Drug Development

- Regulators,
- Professional Associations, and
- Patient Advocacy Groups

Are asking for more diversity in the clinical drug trials.



Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials
Guidance for Industry

FDA Guidance for Industry

Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

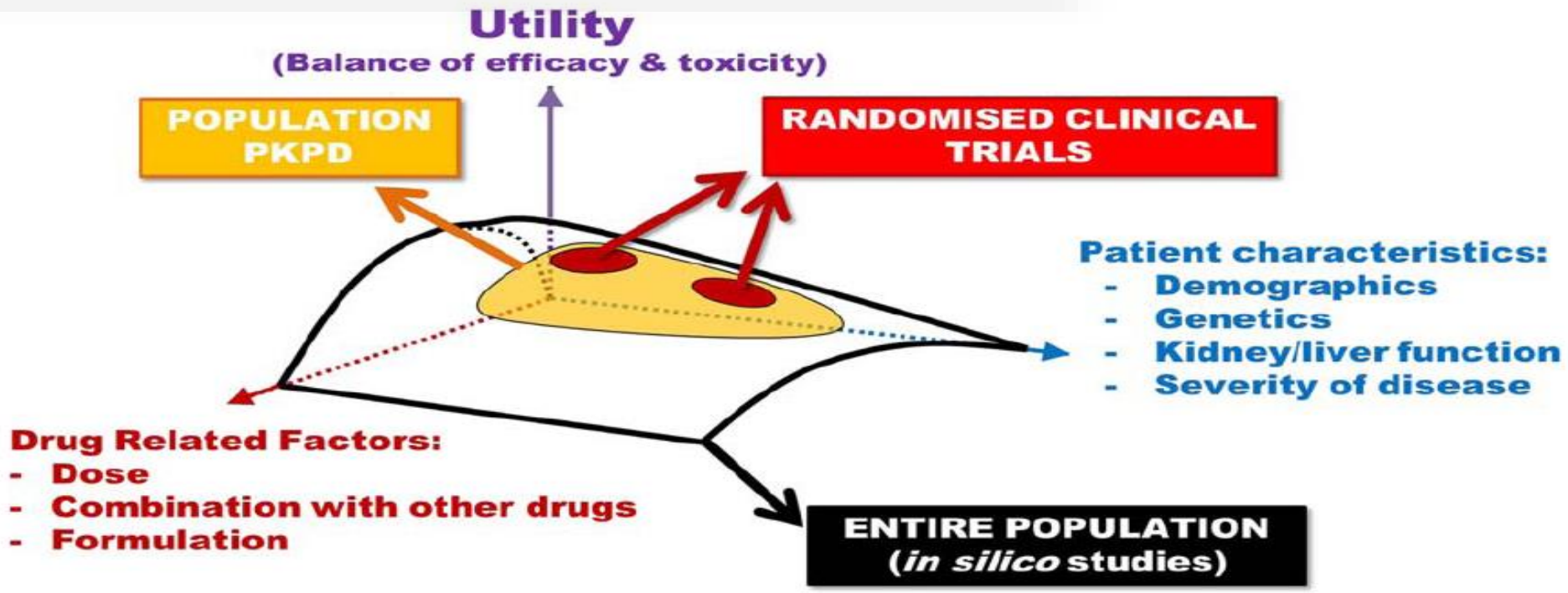
November 2020
Clinical/Medical

POP-PK Has Helped but It Was Not the Panacea

STATE OF THE ART

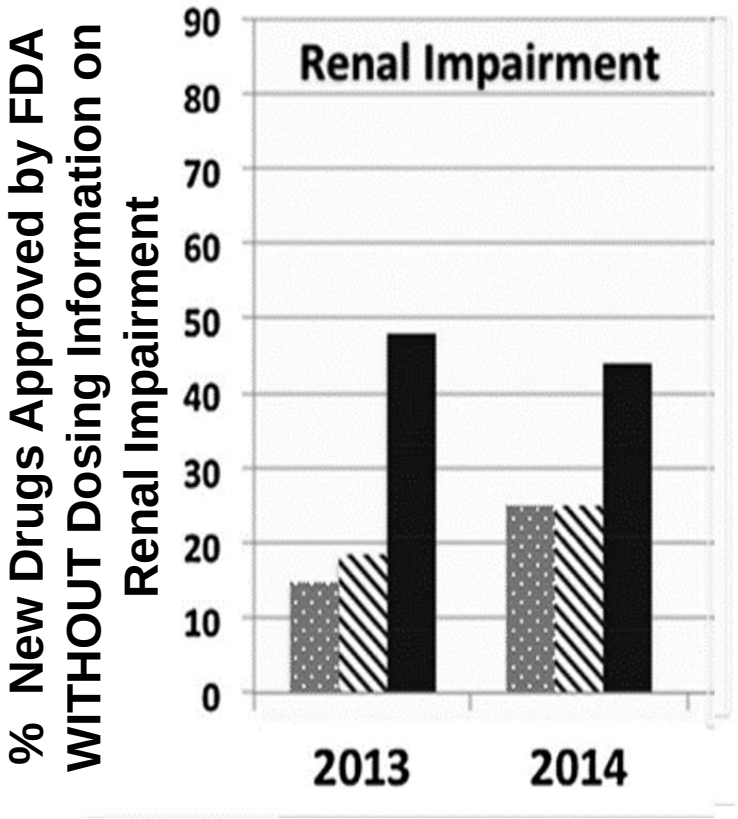
Why Has Model-Informed Precision Dosing Not Yet Become Common Clinical Reality? Lessons From the Past and a Roadmap for the Future

AS Darwich[1], K Ogungbenro[1], AA Vinks[2,3], JR Powell[4], J-L Reny[5,6], N Marsousi[7], Y Daali[5,7], D Fairman[8], J Cook[9], LJ Lesko[10], JS McCune[11], CAJ Knibbe[12], SN de Wildt[13,14], JS Leeder[15,16], M Neely[17], AF Zuppa[18], P Vicini[19], L Aarons[1], TN Johnson[20], J Boiani[21] and A Rostami-Hodjegan[1,21]

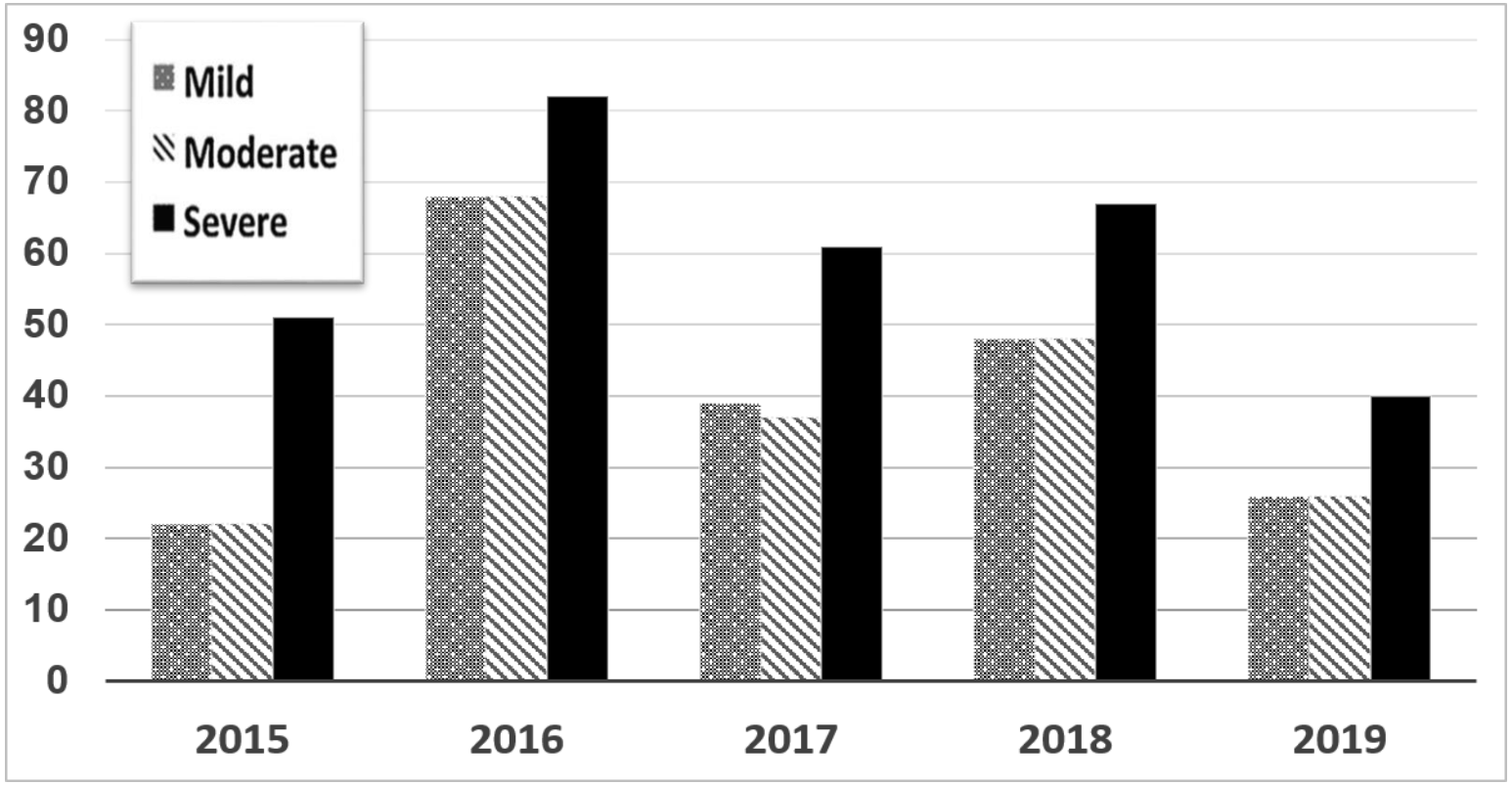


A Key Consequence – Off Label Use of Drugs

Lack of Explicit Dosing Recommendations or Renal Impairment at Point of Entry to Market

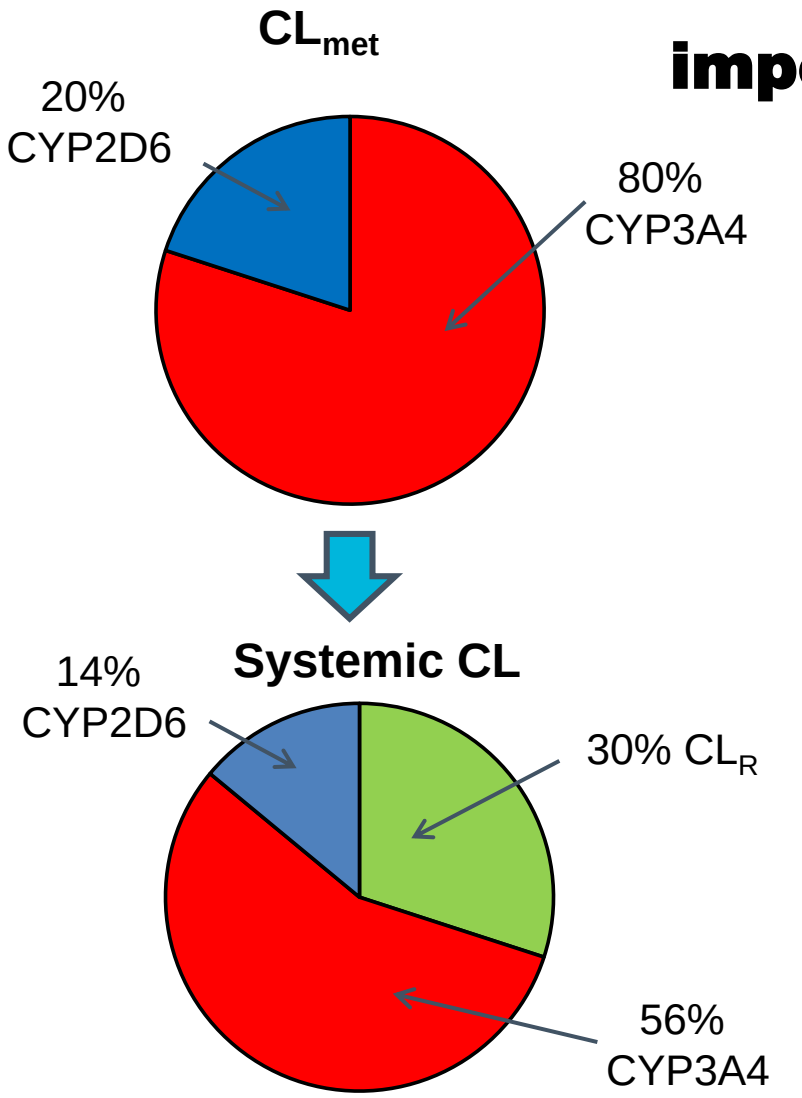


Jadhav et al., 2015



AL-Qassabi J, *Unpublished Survey*

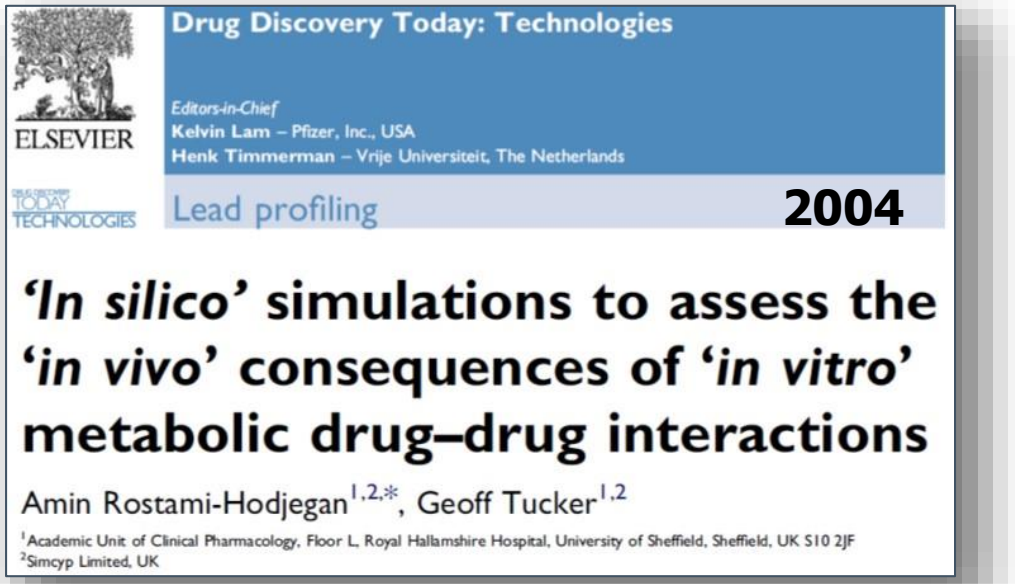
Better (Quantitative) Characterisation of Drugs

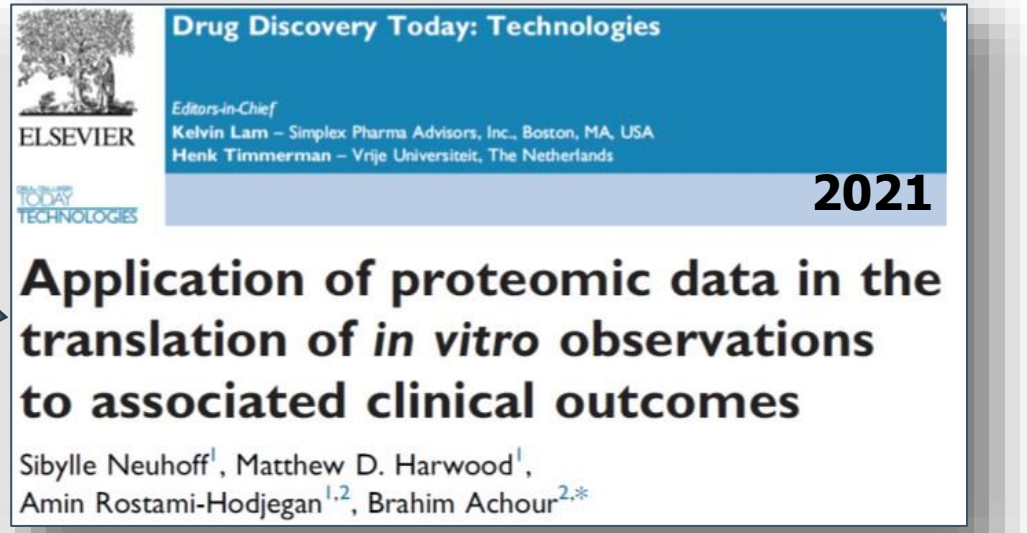


fm CYP3A4 = 0.56

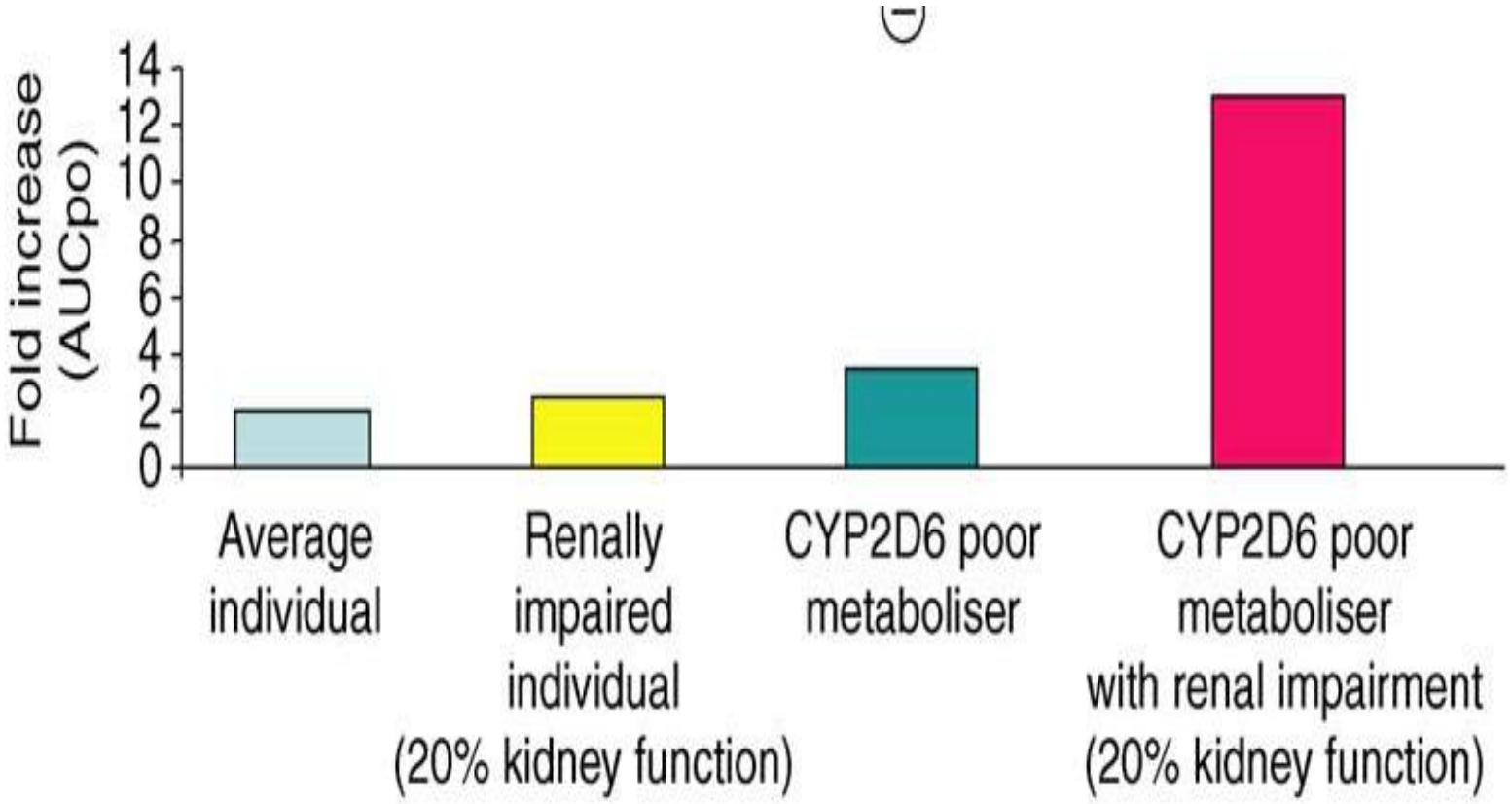
f_m is too important to get it wrong!

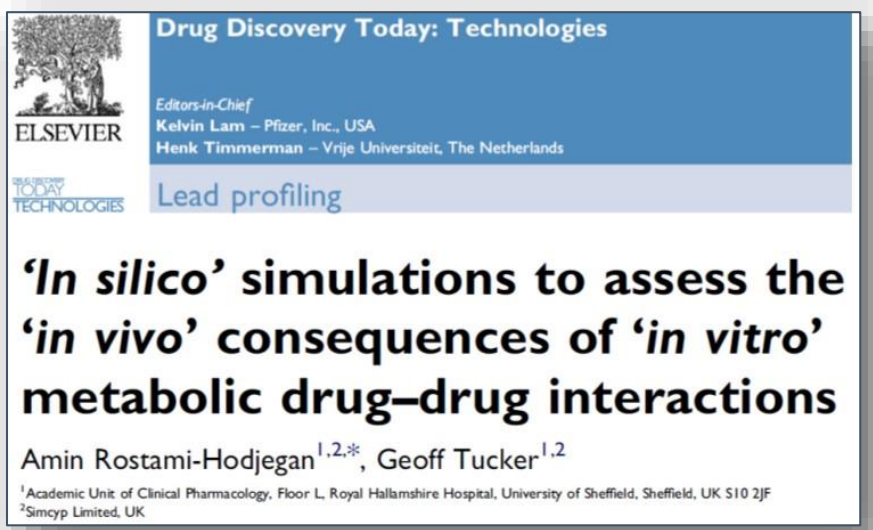
A Quick Recap on a 17-Yrar Long Journey





Theoretical Basis: DDI in Special Populations




Drug Discovery Today: Technologies
Editors-in-Chief
Kelvin Lam – Pfizer, Inc., USA
Henk Timmerman – Vrije Universiteit, The Netherlands
Lead profiling

'*In silico*' simulations to assess the '*in vivo*' consequences of '*in vitro*' metabolic drug–drug interactions

Amin Rostami-Hodjegan[1,2,*], Geoff Tucker[1,2]

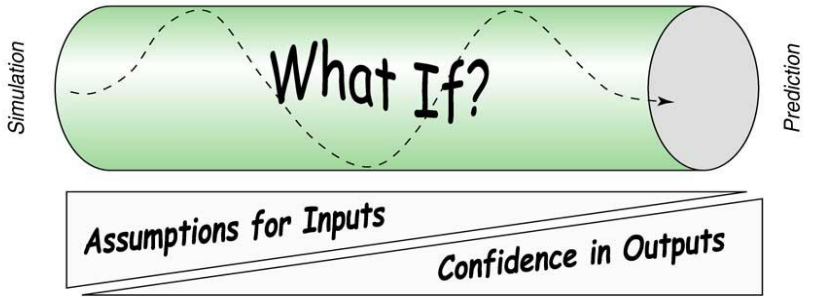
[1]Academic Unit of Clinical Pharmacology, Floor L, Royal Hallamshire Hospital, University of Sheffield, Sheffield, UK S10 2JF
[2]Simcyp Limited, UK

Accumulation of information on compound (as substrate)

Examples:

fm *via* each route in average subject → Population distribution of fm

Estimates of microsomal/plasma binding → Actual fu and fu_{mic}



Examples:

Using single [I] for simulations → Using [I] vs time profile for simulations

Likely mechanism of inhibition → Confirmed mechanism of inhibition

Accumulation of information on compound (as inhibitor)

DDI & Special Populations

Effect of ketoconazole on the pharmacokinetics and safety of telithromycin and clarithromycin in older subjects with renal impairment

J. Shi[1], S. Chapel[1], G. Montay[2], P. Hardy[2], J.S. Barrett[1], D. Sica[3], S.K. Swan[4], R. Noveck[5], B. Leroy[1] and V.O. Bhargava[1]

INT J CLIN PHARM THER 2005

Renal Impairment (Clinical Study)

Renal Impairment (IVIVE/PBPK)

Predicting Drug Interaction Potential With a Physiologically Based Pharmacokinetic Model: A Case Study of Telithromycin, a Time-Dependent CYP3A Inhibitor

MdLT Vieira[1,2], P Zhao[1], EG Berglund[3,4], KS Reynolds[1], L Zhang[1], LJ Lesko[1] and S-M Huang[1]

Biopharm Drug Dispos 2012

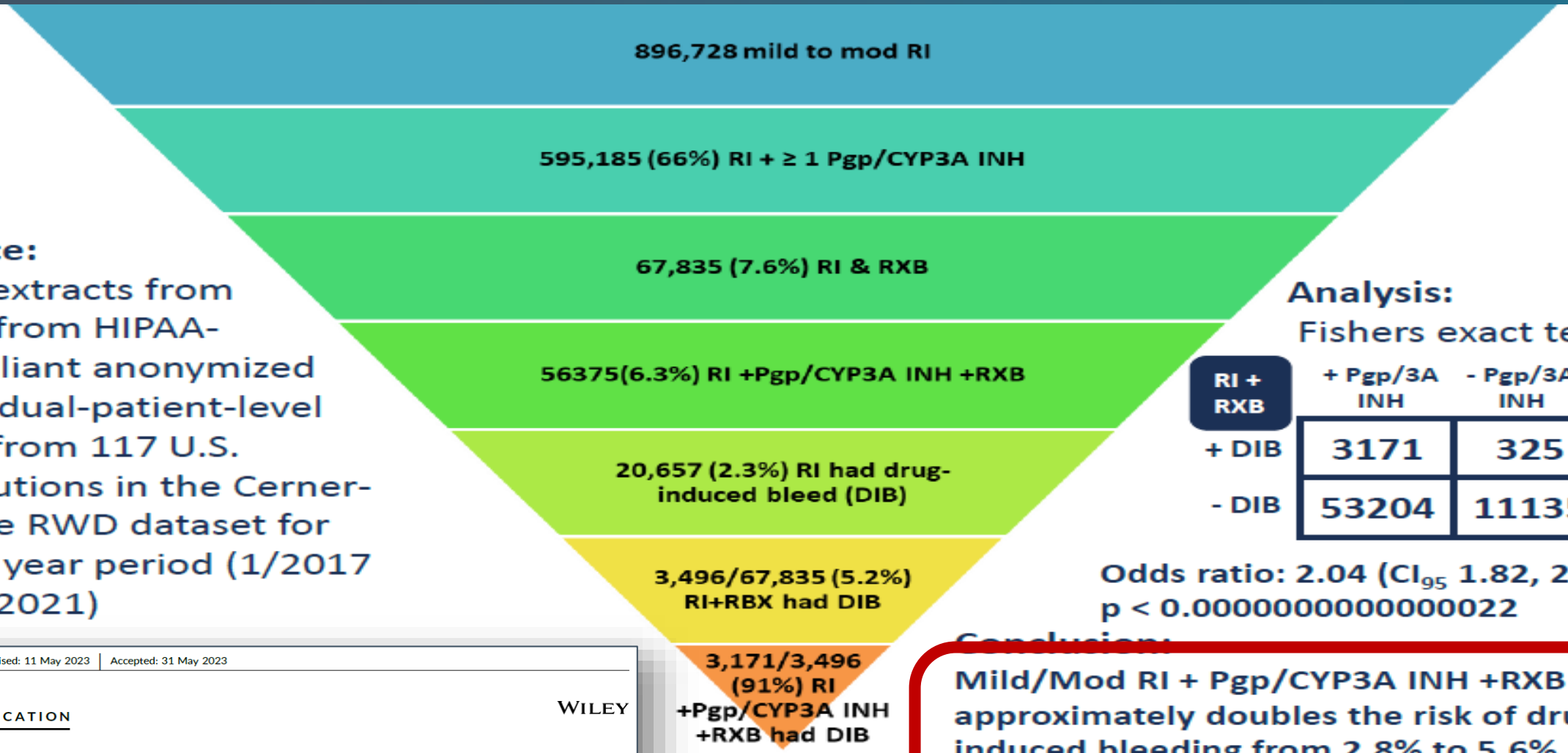
Utility of a physiologically–based pharmacokinetic (PBPK) modeling approach to quantitatively predict a complex drug–drug–disease interaction scenario for rivaroxaban during the drug review process: implications for clinical practice

Joseph A. Grillo[a], Ping Zhao[a,*], Julie Bullock[a], Brian P. Booth[a], Min Lu[b], Kathy Robie-Suh[b], Eva Gil Berglund[c], K. Sandy Pang[d], Atiqur Rahman[a], Lei Zhang[a], Lawrence J. Lesko[a], and Shiew-Mei Huang[a]

CLIN PHARM THER 2012

Drug Label Case (DDI in Renal Impairment

Ten Years Later & Using RWDA (Real World Data Analysis)



Source:

SQL extracts from EHR from HIPAA-compliant anonymized individual-patient-level data from 117 U.S. institutions in the Cerner-Oracle RWD dataset for the 5 year period (1/2017 – 12/2021)

Analysis:

Fishers exact test

RI + RXB	+ Pgp/3A INH	- Pgp/3A INH
+ DIB	3171	325
- DIB	53204	11135

Odds ratio: 2.04 (CI_{95} 1.82, 2.3)

$p < 0.000000000000022$

Conclusion:

Mild/Mod RI + Pgp/CYP3A INH +RXB approximately doubles the risk of drug-induced bleeding from 2.8% to 5.6%

Received: 7 April 2023 | Revised: 11 May 2023 | Accepted: 31 May 2023

DOI: 10.1002/bdd.2369

SHORT COMMUNICATION

WILEY

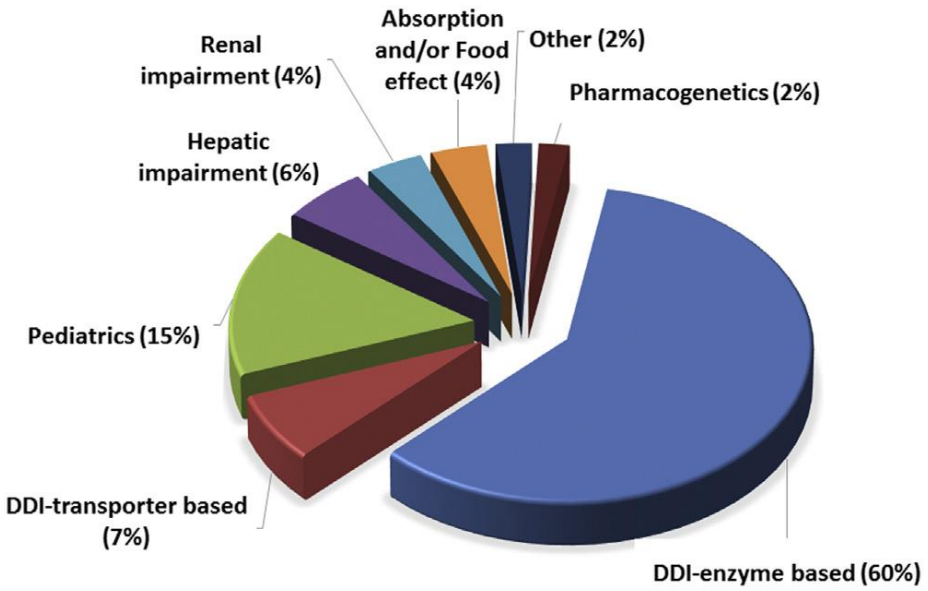
Coming full circle: The potential utility of real-world evidence to discern predictions from a physiologically based pharmacokinetic model

Joseph A. Grillo[1] | Douglas McNair[2] | Ping Zhao[3]

A Reality Now: Simulations Using Virtual Patients As An Alternative To Many Clinical Studies

- >115 Novel Drugs
- >375 Label Claims

Approved by global regulators using the Simcyp Simulator in lieu of clinical studies



ONCOLOGY	AbbVie Venclexta *(venetoclax)*	EMD Serono Tepmetko *(tepotinib hydrochloride)*	Novartis Vijoice *(alpelisib)*
	Agios Tibsovo *(ivosidenib)*	Genentech Alecensa *(alectinib)*	Novartis Rydapt *(midostaurin)*
	Amgen Blincyto *(blinatumomab)*	Genentech Cotellic *(cobimetinib)*	Novartis Tabrecta *(capmatinib)*
	Amgen Lumakras *(sotorasib)*	Genentech Gavreto® *(pralsetinib)*	Novartis Zykadia *(ceritinib)*
	Ariad Alunbrig *(brigatinib)*	Genentech Polivy *(polatuzumab vedotin-piiq)*	Novartis Jakavi *(ruxolitinib)*
	Ariad (Takeda) Iclusig *(ponatinib)*	Genentech Rozlytrek *(entrectinib)*	Pfizer Daurismo *(glasdegib)*
	AstraZeneca Calquence *(acalabrutinib)*	Incyte Pemazyre *(pemigatinib)*	Pfizer Ibrance® *(palbociclib)*
	AstraZeneca Lynparza *(olaparib)*	Janssen Balversa *(erdafitinib)*	Pfizer Bosulif *(bosutinib)*
	AstraZeneca Tagrisso *(osimertinib)*	Janssen Erleada *(apalutamide)*	Pfizer Lorbrena *(lorlatinib)*
	AstraZeneca Truqap® *(capivaserib)*	Lilly Retevmo *(selpercatinib)*	Pharmacyclics Imbruvica *(ibrutinib)*
	Beigene Brukinsa *(zanubrutinib)*	Lilly Verzenio *(abemaciclib)*	Puma Nerlynx® *(neratinib)*
	Biohaven Nurtec *(rimegepant)*	Loxo Jaypirca *(pirtobrutinib)*	Sanofi Jevtana *(cabazitaxel)*
	BluePrint Medicines Ayvakit *(avapritinib)*	Loxo Oncology Vitrakvi *(larotrectinib)*	Seattle Genetics Tukysa *(tucatinib)*
	Celgene Inrebic *(fedratinib hydrochloride)*	Menarini/Stemline Orserdu *(elacestranto)*	Spectrum Beleodaq *(belinostat)*
	Daiichi Sankyo Turalio *(pexidartinib)*	Mirati Krazati *(adagrasib)*	Springworks Ogsiveo® *(nirogancent)*
	Daiichi Sankyo Ezharmia *(valmetostat tosilate)*	Novartis Farydak *(panobinostat)*	Takeda Exkivity *(mobocertinib)*
	Daiichi Sankyo Vanflyta® *(quizartinib dihydrochloride)*	Novartis Kisqali *(ribociclib succinate)*	Takeda Fruzaqla® *(fruquintinib)*
	Deciphera Qinlock *(ripretinib)*	Novartis Scemblix *(asciminib)*	Taiho Lytgobi *(futibatinib)*
	Eisai Lenvima *(lenvatinib)*	Novartis Odomzo *(sonidegib)*	Verastem Copiktra *(duvelisib)*
RARE DISEASE	Agios Pyrukynd *(mitapivat)*	Intercept Ocaliva *(obeticholic acid)*	Peloton/Merck Welireg *(belzutifan)*
	AkaRx (Eisai) Doptelet *(avatrombopag maleate)*	Ipsen Sohonus® *(palovarotene)*	PTC Therapeutics Emflaza *(deflazacort)*
	AstraZeneca Koselugo *(selumetinib)*	Kadmon Rezurock *(belumosudil)*	Sanofi Genzyme Cerdelga *(eliglustat tartrate)*
	Aurinia Lupkynis *(voclosporin)*	Merck Welireg *(belzutifan)*	Travere Filspari *(sparsentan)*
	Genentech Enspryng *(satralizumab)*	Mirum Livmarli *(maralixibat)*	Vertex Symdeko *(tezacaftor/ivacaftor)*
	Genentech Evrysdi *(risdiplam)*	Mitsubishi Tanabe Dysval *(Valbenazine)*	Vertex Trikafta *(elexacaftor/ivacaftor/tezacaftor)*
	Global Blood Therapeutics Oxbryta *(voxelotor)*	Novartis Isturisa *(osilodrostat)*	
CENTRAL NERVOUS SYSTEM	AbbVie Rinvoq *(upadacitinib)*	Eisai Dayvigo *(lemborexant)*	Lilly Reyvow *(lasmiditan succinate)*
	AbbVie Qulipta *(atogepant)*	Idorsia Quviviq *(daridorexant)*	Novartis Mayzent *(siponimod fumaric acid)*
	Alkermes Aristada *(aripiprazole lauroxil)*	Janssen Ponvory *(ponesimod)*	Pfizer Zavzpret *(zavegepant)*
	Alkermes Lybalvi *(olanzapine/samidorphan)*	Kyowa Kirin Nourianz *(istradefylline)*	UCB Briviact *(brivaracetam)*
INFECTIOUS DISEASE	Gilead Vexlury *(remdesivir)*	Merck Prevymis *(letermovir)*	Pfizer Paxlovid® *(nirmatrelvir, ritonavir)*
	Gilead Veklury *(remdesivir)*	Nabriva Xenleta *(lefamulin acetate)*	Tibotec Edurant *(rilpivirine)*
	Janssen Olysio *(simeprevir)*	Novartis Egaten *(triclabendazole)*	ViiV Cabenuva Kit *(cabotegravir/rilpivirine)*
	Merck Pifeltro *(doravirine)*		
GASTROENTEROLOGY	AstraZeneca Farxigo *(dapaglifoxin)*	Phathom Voquezna TriplePak *(vonoprazan/amoxicillin/clarithromycin)*	Shire Motegrity *(prucalopride)*
	AstraZeneca Movantik *(naloxegol)*	Shionogi Symproic *(naldemedine)*	
	Helsinn Akynzeo *(fosnetupitant/palonosetron)*		
CARDIOVASCULAR	Actelion (J & J) Opsumit *(macitentan)*	Johnson & Johnson Xarelto *(rivaroxaban)*	
	BMS Camzyos *(mavacamten)*	Pfizer Revatio *(sildenafil)*	
ENDOCRINE	AbbVie Orilissa *(elagolix)*	Janssen Invokana *(canagliflozin)*	Merck Steglatro *(ertugliflozin)*
	Astellas Veozah® *(fezolinetant)*	Lilly Olumiant *(baricitinib)*	
	Esperion Nexetol *(bempedoic acid)*	Lilly Mounjaro *(tirzepatide)*	
OTHER	Galderma Aklief *(trifarotene)*	Takeda Livtencity *(maribavir)*	

Updated March. 2024

Grimstein et al 018, *J Pharm Sci*

Focusing on Lessons Learnt

Retrospective **Prospective**

Past **Present** **Future**

(1) Vision was there but many things needed to change (Philosophy/Practice),

(2) Two main building blocks involved “”Population” and “Compound” files,

(3) Regulatory push for addressing unmet needs vis new approaches helped,

(4) The starting point was in areas where there were no other alternatives,

(5) This was extended to areas when the clinical studies were cumbersome,

(6) With growing confidence, PBPK/IVIVE is now an alternative to many studies.

Points of Debate

In Vitro vs In Vivo

Open Source vs Open Science

Assessing 1000's Lines of Program for Open Source-Code Models for Every Submission?!?

Alternative Option:

"GLASS BOX"

Full Transparency

via

Model Qualification (Master File)

Peer Review by Experts, Scientific Publications, Public Workshops, and Full Implementation Documents which Are Accessible to Regulators.

Quality-Assured / Version-Controlled

(NOT *EVERYONE* CAN MODIFY THE CODE!_

STATE OF THE ART

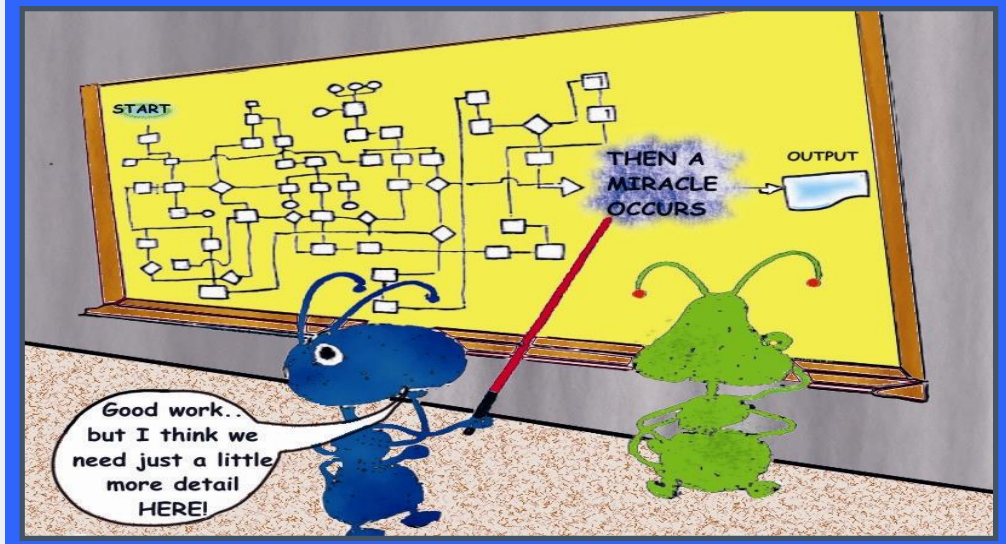
Reverse Translation in PBPK and QSP: Going Backwards in Order to Go Forward With Confidence

Amin Rostami-Hodjegan[1,2]

Clin Pharm Ther 2018

NO TO

BLACK BOX



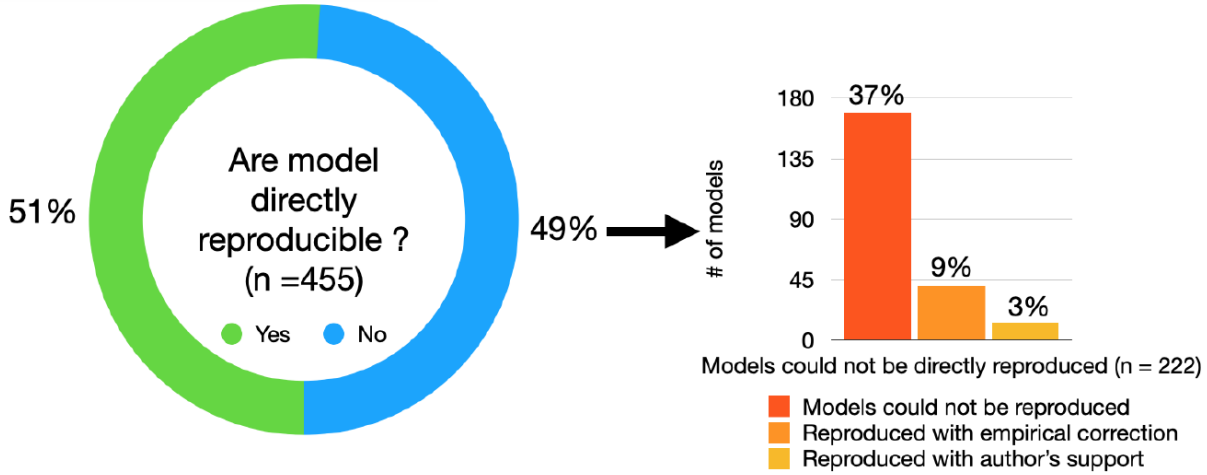
Counter-Intuitive Nature of Open Source-Code Models

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"

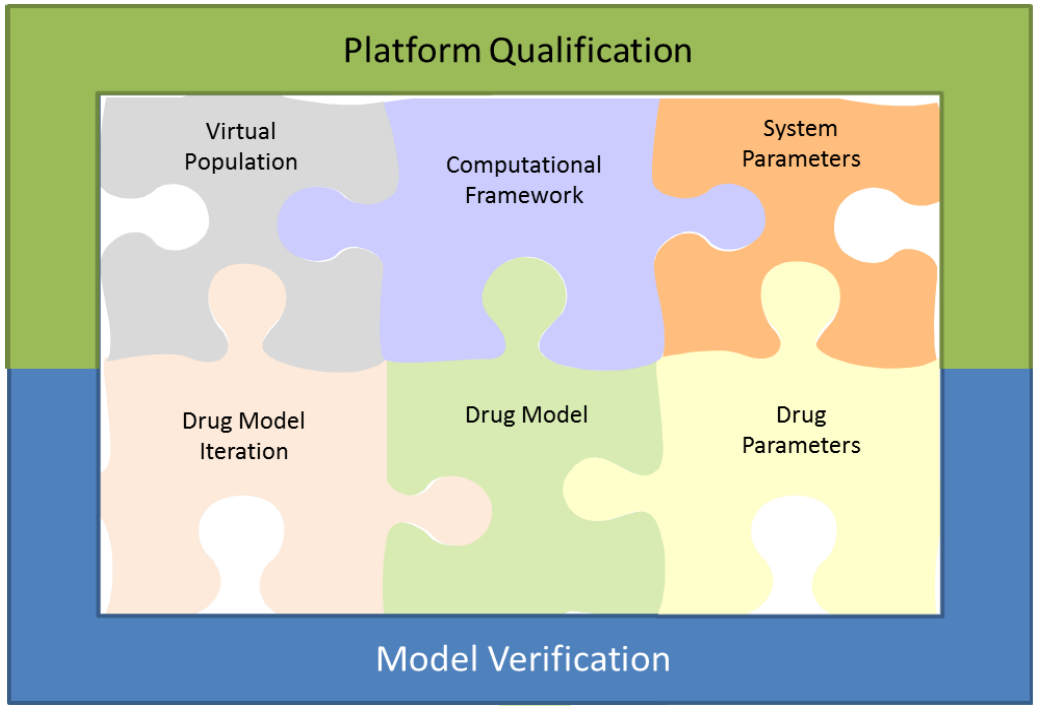
Qualification/Verification/Validation/Credibility

Validation of Code

vs

Validation of Application

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

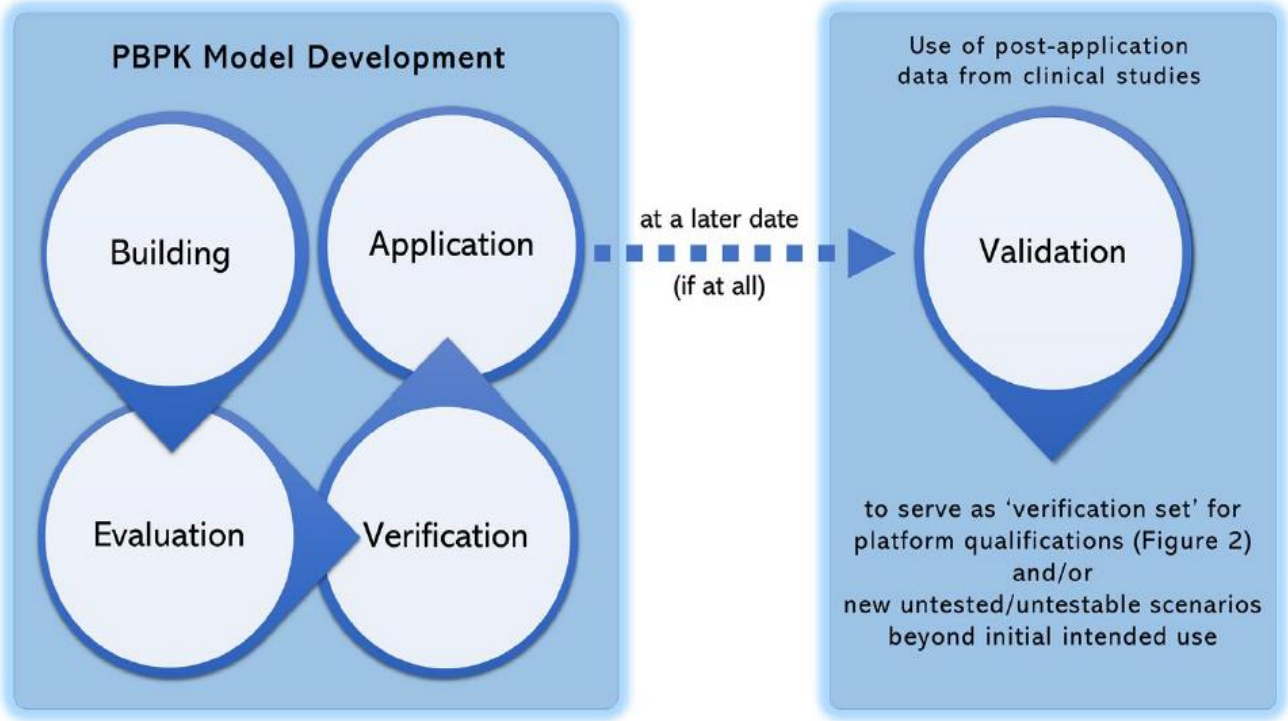


2022; 39(8):1729-1748
https://doi.org/10.1007/s11095-022-03250-w
Check for updates

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



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

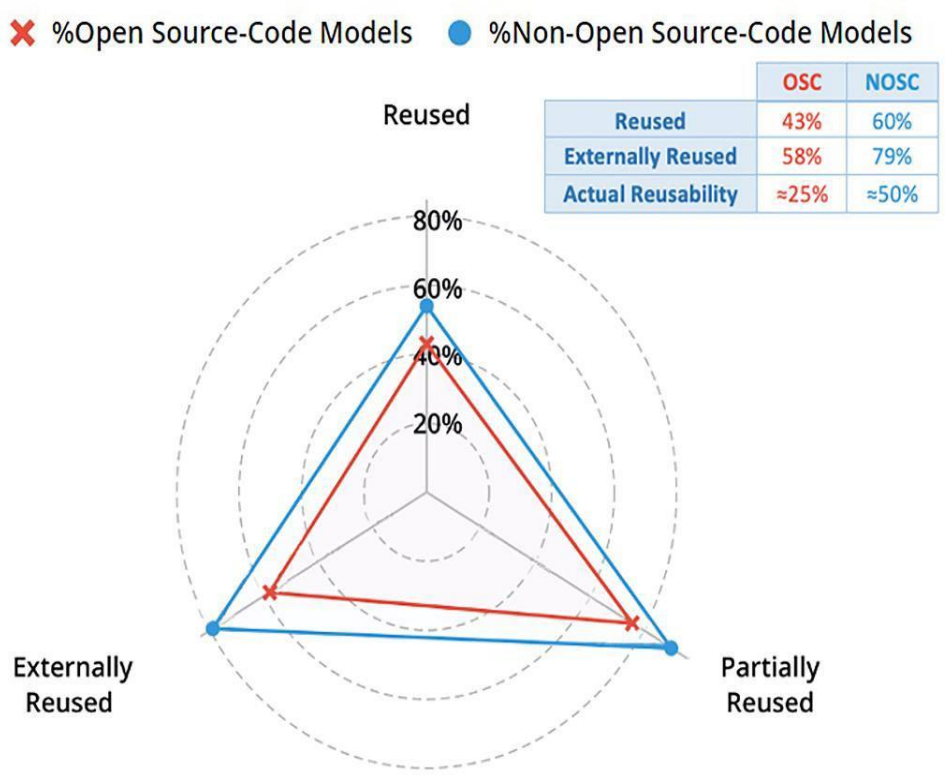
In-Depth Analysis of Patterns in Selection of Different Physiologically-Based Pharmacokinetic Modelling Tools:

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

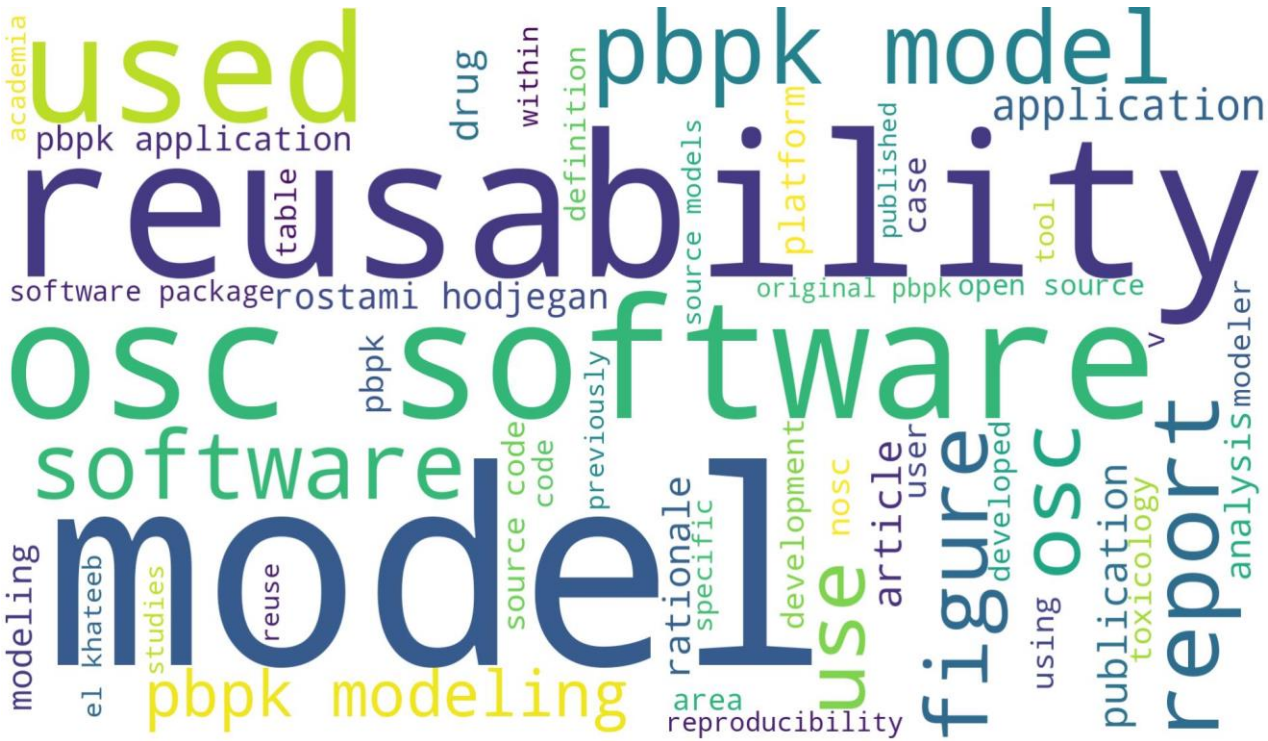
Part II - Assessment of Model Reusability and Comparison Between Open and Non-Open Source-Code Software

Biopharmaceutics & Drug Disposition

Rajput et al
Adibani et al
Biopharm Drug Dispos 2023 44(3):274-285 - 44(4):292-300

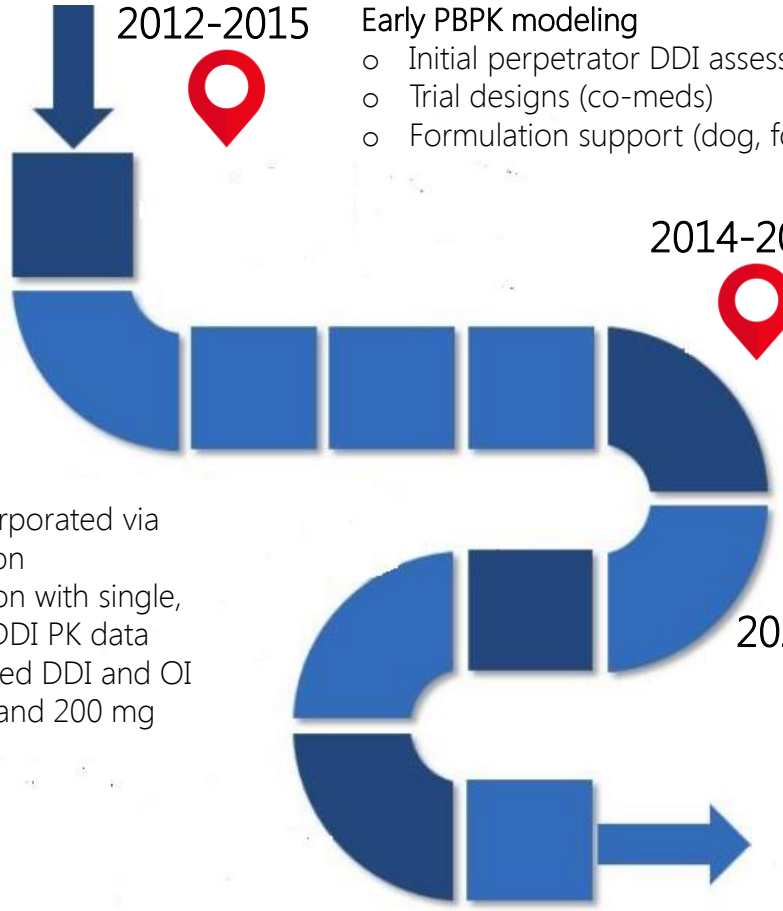


	OSC	NOSC
Reused	43%	60%
Externally Reused	58%	79%
Actual Reusability	≈25%	≈50%



Model Reusability Advantage for Drug Life Cycle

A Public Case Example by Novartis: PBPK Support for Asciminib from Preclinical Development to NDA



2012-2015 Early PBPK modeling
- Initial perpetrator DDI assessments (CYP3A DDI)
- Trial designs (co-meds)
- Formulation support (dog, food effect)

2014-2019 Refined PBPK model
- PK characterization
- Food effect
- Support of cDDI plan–fmCYP confirmed
- CSF to FMI support
- Support of organ impairment studies

2019-2020 Final PBPK model
- PK nonlinearity incorporated via transporter saturation
- Final model validation with single, multiple dose PK, cDDI PK data
- Simulation of untested DDI and OI scenarios at 80 mg and 200 mg

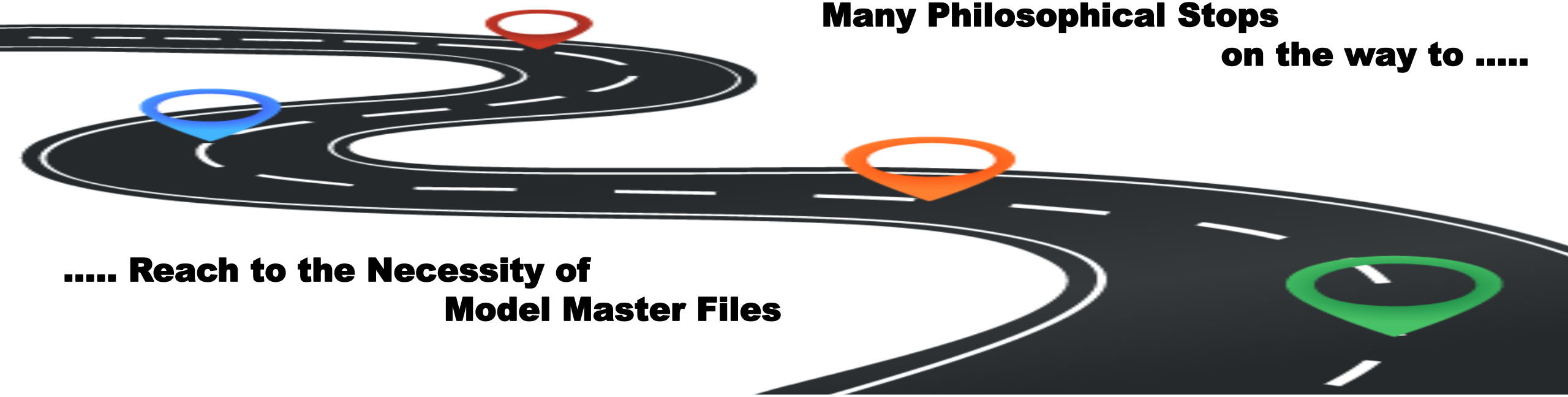
2021 - now NDA submission and FDA approval
- PBPK impacted USPI
- >10 clinical pharmacology studies waived
- PBPK addressed IRs and 4 PMC/PMR - no request for clinical study
- 1st time eData submission in JP – PMDA

The Road for Natural Progression of Systems Model to Model Master File (MMF)

Research Frontier

Routine Scaled Up Usage

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



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

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.

GISim

Simcyp Simulator

GastroPlus

Innovative Tools for Oral Biopharmaceutics

OrBiTo API Data Files

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

Filtering and grouping based on parameters of interest.

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

Contents lists available at ScienceDirect

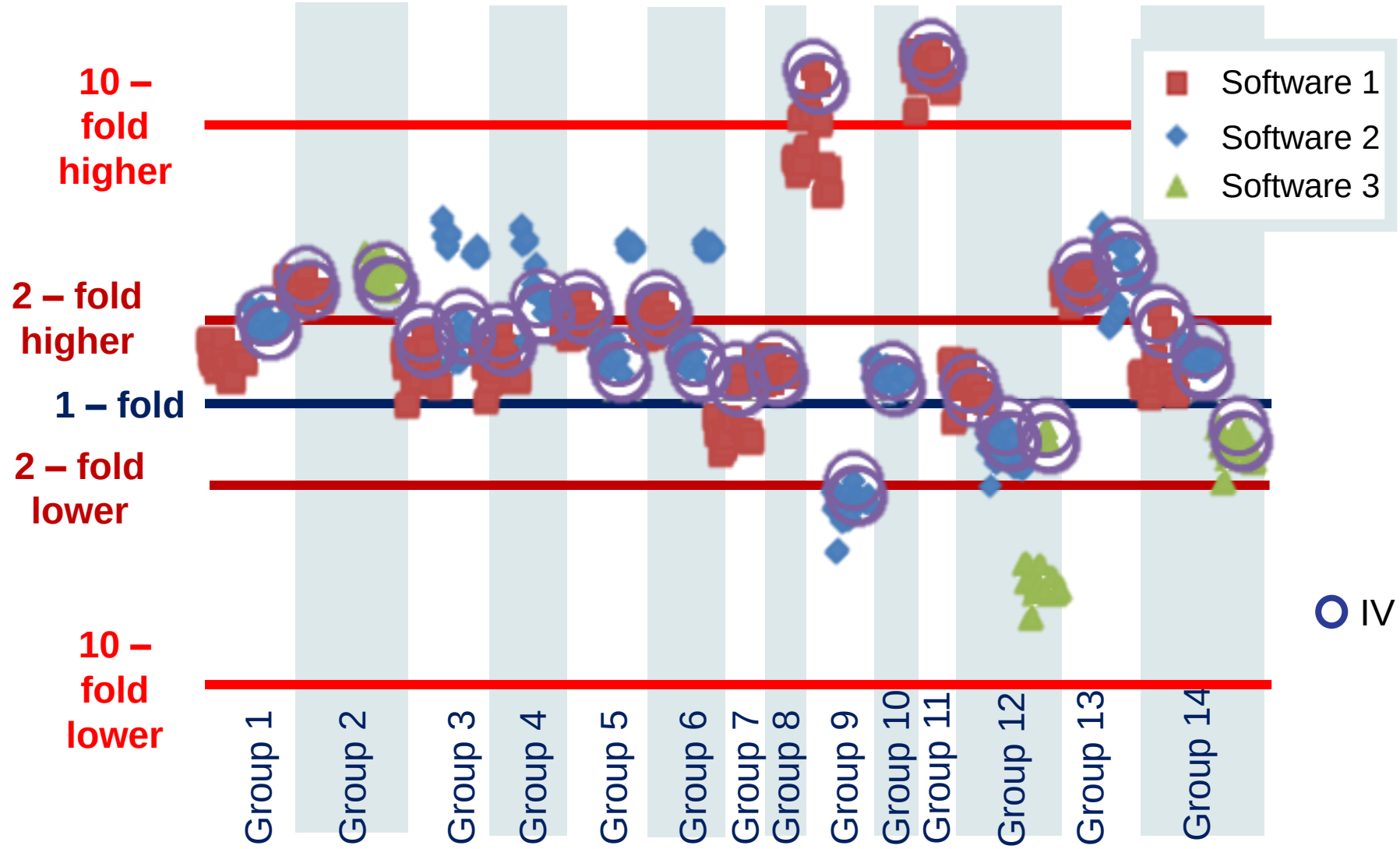
Computer Methods and Programs in Biomedicine

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]

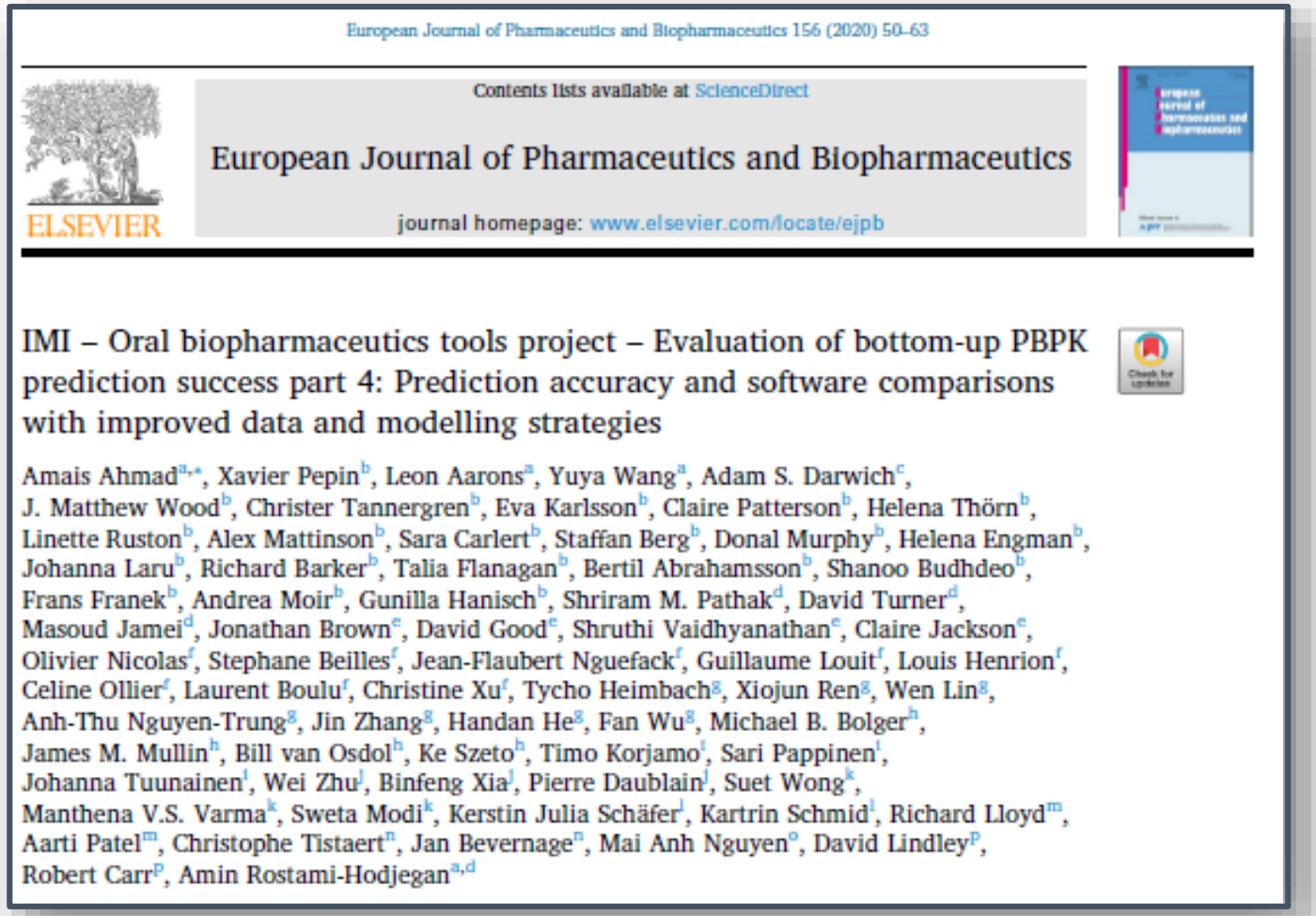
Fold error of AUC last predictions for API A2733



A FOOL with TOOL, is still a FOOL!

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

Focusing on Lessons Learnt

Retrospective **Prospective**

Past **Present** **Future**

(1) Mission was never about “software”, but about “placeholder” for knowledge,

(2) The systems/drug information come from both *in vitro* & *in vivo* studies,

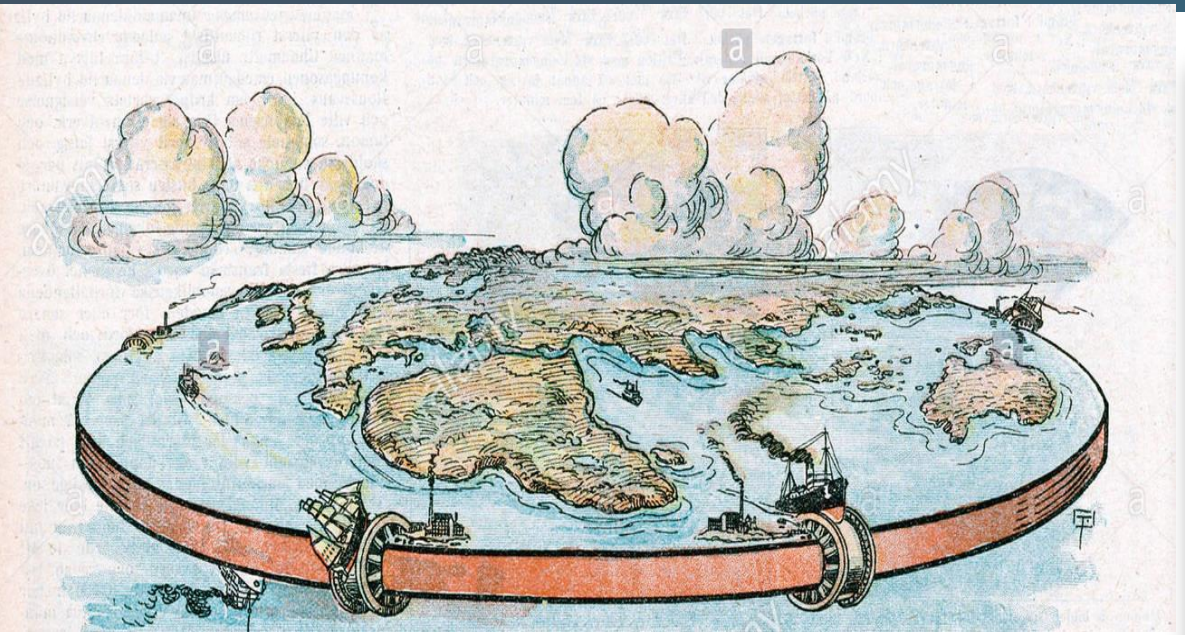
(3) Once settled on verified models, they are locked for version control (MMF),

(4) The higher reusability of closed systems outweighs open-source code mode,

(5) Credible modeller (F1) build models but they can be applied by wider groups,

(6) Education of modeler plays higher importance than the tool that they use!

PBPK/IVIVE Entering Uncharted Territories - 2020



JCP 2020

ACCP

Supplement Article

Physiologically Based Pharmacokinetics as a Component of Model-Informed Drug Development: Where We Were, Where We Are, and Where We Are Heading

The Journal of Clinical Pharmacology 2020, 60(S1) S12–S16

DOI: 10.1002/jcph.1654

Amin Rostami-Hodjegan, PhD, PharmD, FCP[1,2] and Stephen Toon, PhD[2]

PBPK ship sailing to Uncharted Waters

Until recently, there was *no feasible* way to obtain individual information on abundance of proteins relevant to the fate of the drug ..... The invention of *liquid biopsy* .... has changed the paradigm and has brought us one step closer to using PBPK as the basis for creating

"Virtual Twins"

and consequently to individual dosing.

Virtual Twins: Understanding the Data Required for Model-Informed Precision Dosing

CPT 2020

Thomas M. Polasek[1,2,3,*] and Amin Rostami-Hodjegan[1,4]

2018 Regulatory Application & Predictive Performance

FDA

- Higher confidence, greater experience, fewer knowledge gaps, higher likelihood of acceptability
- Some experience, knowledge gaps identified, likelihood of acceptability on case-by-case basis
- Limited experience, significant knowledge gaps, low likelihood of acceptability at this time

Drug Interactions

- **CYP450 Drug as Substrate**
  - Inhibitor interaction prediction with higher potency clinical data verification
  - Concern with Rifampin under prediction
  - Dual enzyme time dependent inhibitor and inducer prediction not mature
- **CYP450 Drug as Perpetrator**
  - Negative interaction prediction
  - Some experience with positive interaction prediction, but knowledge gaps exist
- **Transporter Systems**
  - Some experience with Pgp and combined Pgp/ CYP3A interaction prediction and negative interaction prediction for basolateral uptake transporters, but knowledge gaps exist
  - Intestinal BCRP, hepatic OATP1B1/3, NTCP, MRP2, OATPs, and renal OATs and OCT2 positive prediction not mature
  - in vitro/in vivo extrapolation for solute carriers complex
- **Phase II Metabolism**
  - Some experience with UGT's, but prediction not mature

Specific Populations

- **Pediatrics**
  - Some experience, but knowledge gaps exist
    - Greater utility likely in age ≤ 2 years
- **Renal or Hepatic Impairment**
  - Some experience, but prediction not mature
- **Pregnancy, ethnicity, geriatrics, obesity, & disease states**
  - Prediction not mature

Other Areas

- **Food, formulation, & tissue concentration**
  - Prediction not mature
- **pH effect on Fa**
  - Some experience, but knowledge gaps exist
- **Absorption**
  - BCS Class I drugs
  - Some experience with BCS Class II, but knowledge gaps exist
  - BCS Class III and IV prediction not mature

Adapted from:

Wagner, C., et al. CPT: pharmacometrics & systems pharmacology 2015; 4: 226-230
Grimstein, M., et al. J Pharm Sci. 2019; 108(1):21-25

2023 Regulatory Application & Predictive Performance

FDA

- Higher confidence, greater experience, fewer knowledge gaps, higher likelihood of acceptability
- Some experience, knowledge gaps identified, likelihood of acceptability on case-by-case basis
- Limited experience, significant knowledge gaps, low likelihood of acceptability at this time

Drug Interactions

CYP450 *Drug as Substrate*

- Inhibitor interaction prediction with higher potency clinical data verification
- Some experience with dual enzyme time dependent inhibitor and inducer prediction, but knowledge gaps exit

CYP450 *Drug as Perpetrator*

- Negative interaction prediction for inhibition
- Some experience with positive interaction prediction on CYP3A pathway, but knowledge gaps exist
- Some experience with interaction prediction for induction on CYP3A pathway, but significant knowledge gaps exist on the in vitro/in vivo extrapolation of induction data

Transporter Systems

- Some experience with P-gp and combined P-gp/ CYP3A interaction prediction, but knowledge gaps exist
- Some experience with negative interaction prediction on intestinal BCRP and renal OATs, but knowledge gaps exist
- Hepatic OATP1B1/3, NTCP, MRP2, and renal MATEs and OCT2 interaction prediction is not mature. Potential for combining endogenous biomarker data

Phase II Metabolism

- Some experience with UGT for negative interaction prediction, but knowledge gaps exist

Specific Populations

Pediatrics

- Some experience, but knowledge gaps exist

Renal or Hepatic Impairment

- Very few RI submissions and the available PBPK submission did not provide adequate validation
- Some HI experience, but model performance varies.

Pregnancy, Lactation, Ethnicity, Geriatrics, Obesity, & Disease States

- Some pregnancy experience, but knowledge gaps exist
- Prediction for lactation & other intrinsic factors not mature

Other Areas

Food, formulation, & tissue concentration

- Some tissue concentration experience but need to review case-by-case
- Limited gastric emptying time experience with GLP-1 mediated gastric empty delay
- Limited formulation experience, limited to negative prediction and knowledge gaps exist
- Food effect prediction is not mature for positive interaction

pH effect on Fa

- Some experience, limited to negative prediction

Absorption

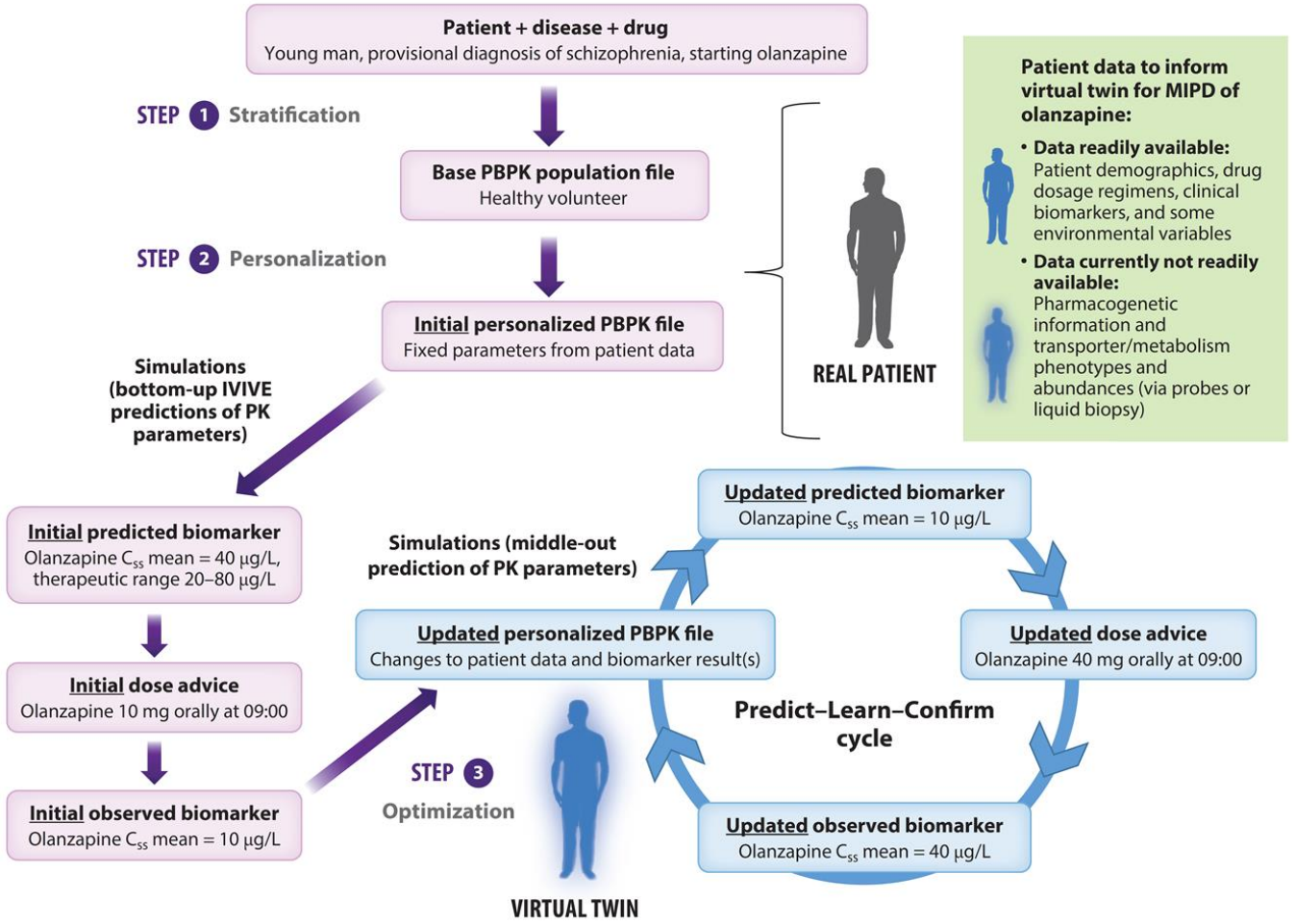
- BCS Class I drugs
- Some experience with BCS Class II, but knowledge gaps exist
- BCS Class III and IV prediction not mature

Characterisation: Centre Piece of MIPD

Annual Review of Pharmacology and Toxicology

Model-Informed Precision Dosing: Background, Requirements, Validation, Implementation, and Forward Trajectory of Individualizing Drug Therapy

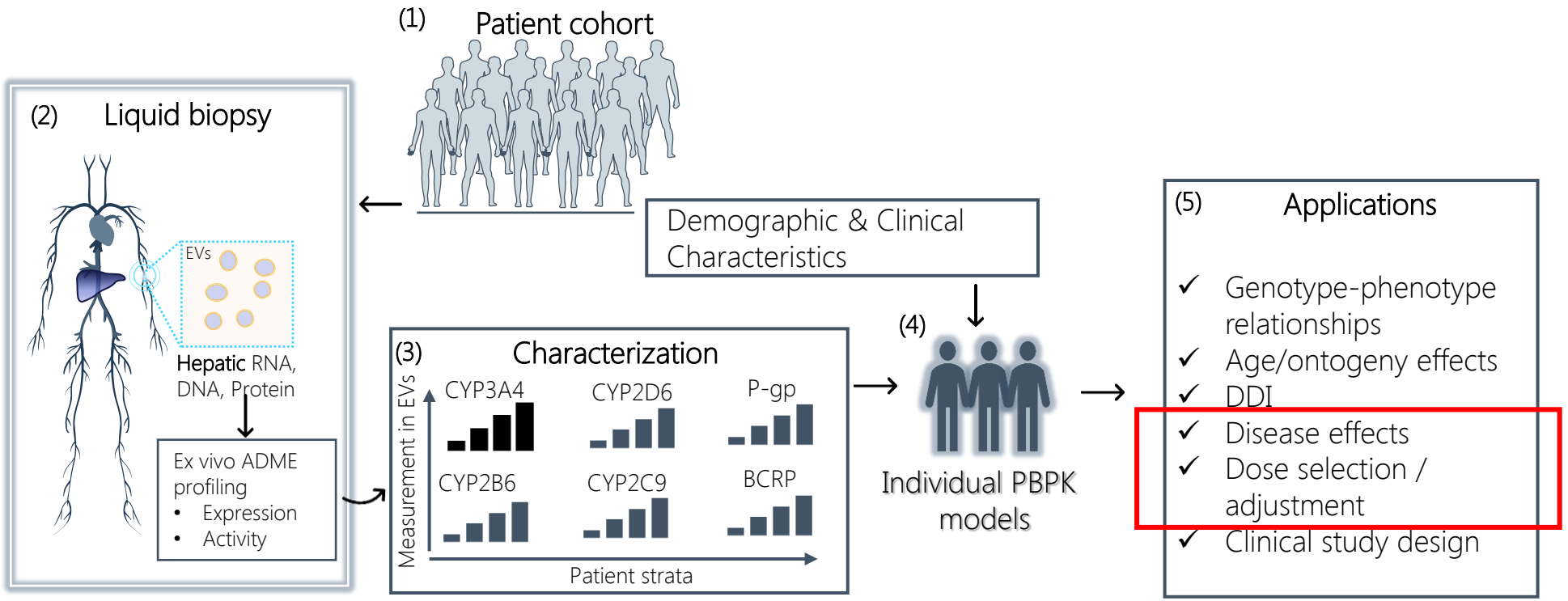
Darwich et al., 2020, AR P&T, 61:225-245



- **MIPD *(Virtual Twins)* has not been applied because its requirements have not been met, particularly systems data at the individual patient level**

- **How can this work? By defining attributes of metabolism and transport in the liver using a method of sampling that is minimally invasive**

‘Liquid Biopsy’ with Virtual Twins: Implementation



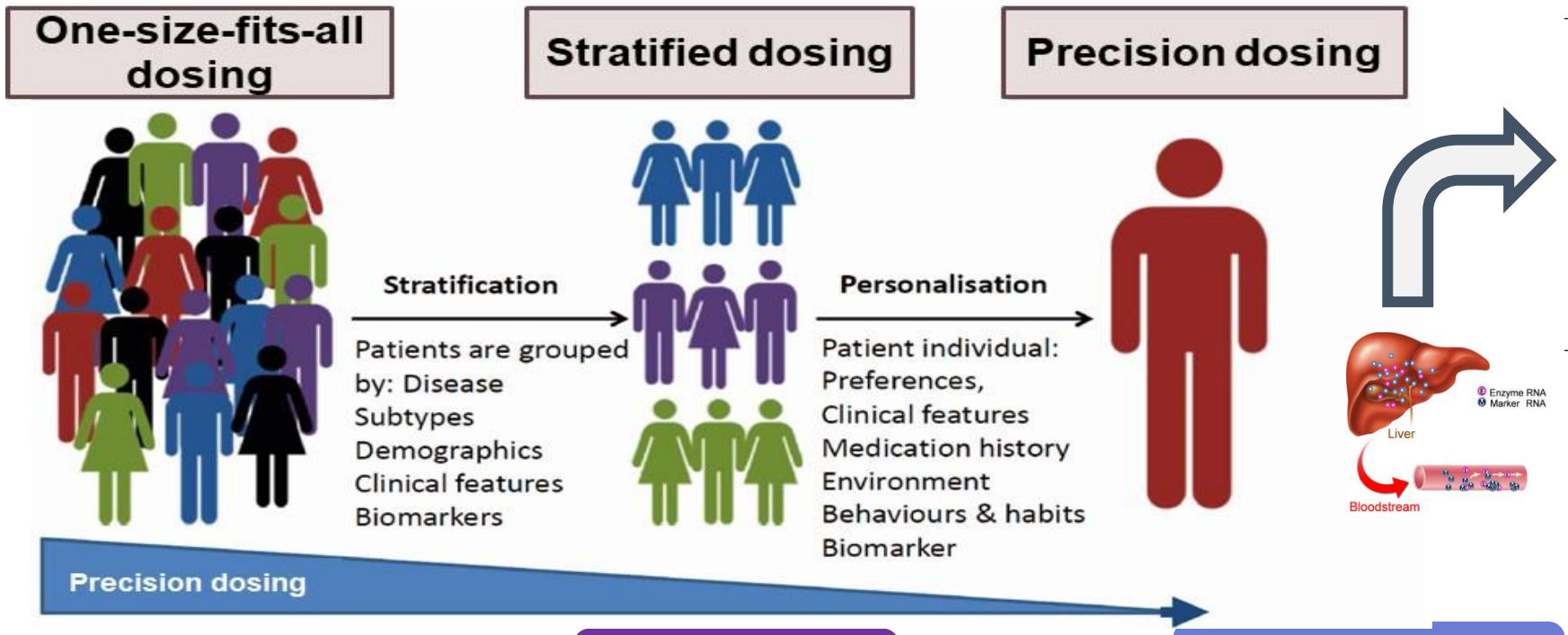
Jackson, Achour et al., 2023, DMD, In Press

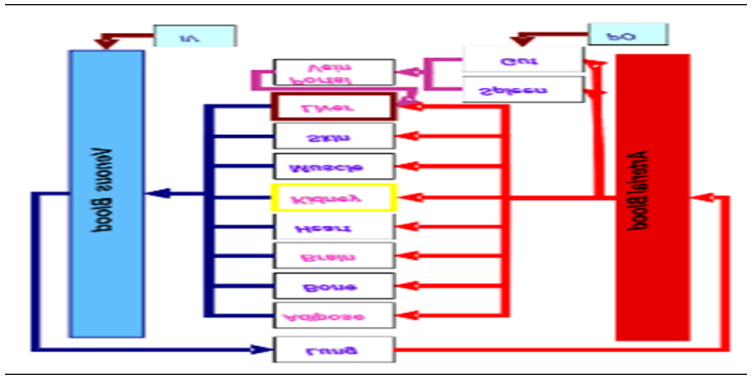
<u>Modelling Midazolam exposure:</u> Four base models on Simcyp® v21 R1 (healthy, mild, moderate, severe RI)

Individualized into 25 Virtual Twin models with (*demography, renal function and <u>liquid biopsy data</u> for CYP3A and UGT1A4*)

Rostami-Hodjegan et al., 2024, *Under Review - CPT*

Virtual Twin: "Not All About Genetics"





Raw Material Warehouse

PBPK today → PBPK + Liquid Biopsy

Defining the Need and Approach to Deliver Individualized Drug Dosing in the Real World Setting

August 12ft, 2019

FDA White Oak Campus: Great Room

3D Printing of Dosage

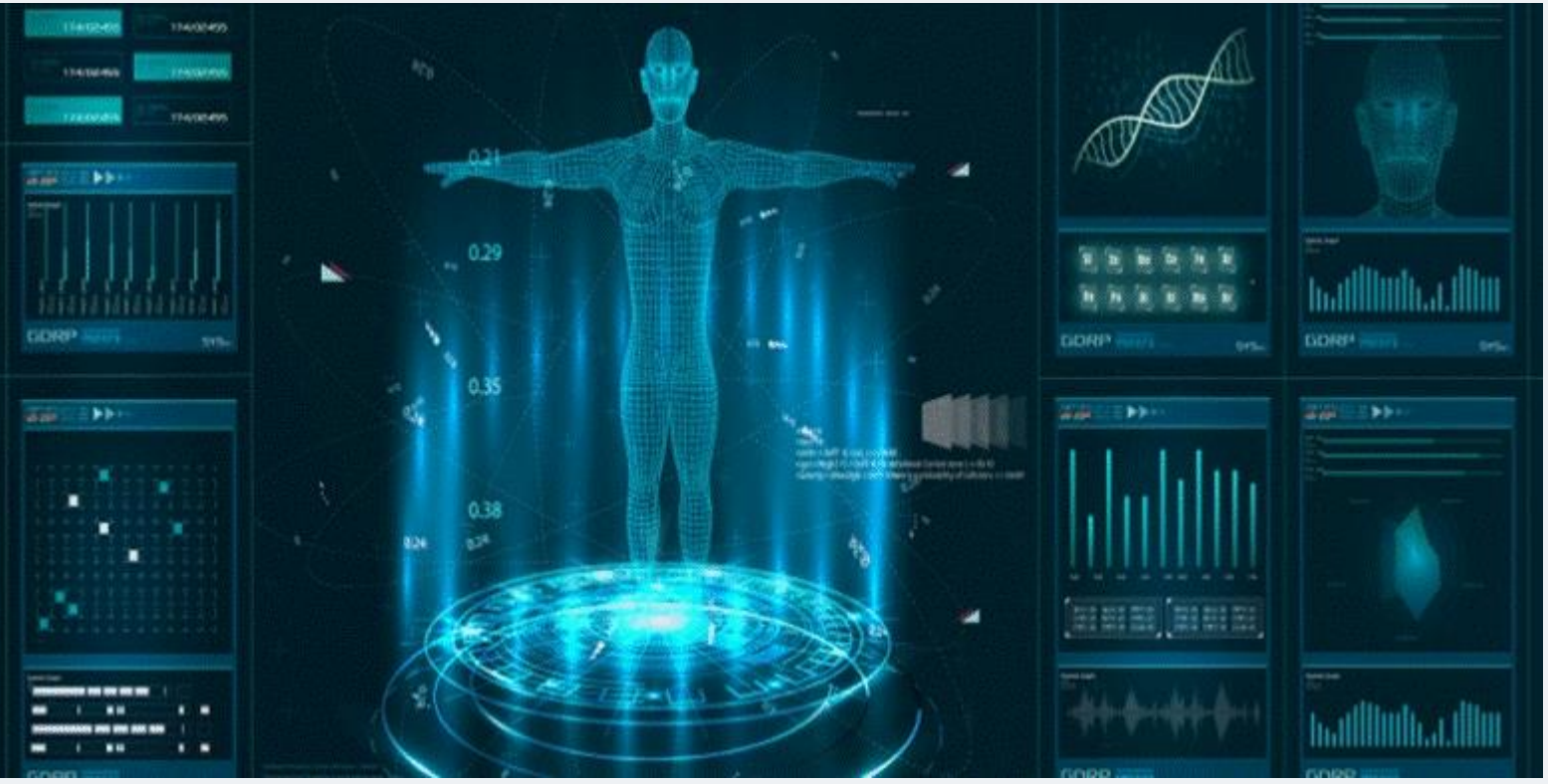
Home Delivery

Polasek et al (2018) Precision Dosing in Clinical Medicine: present and future, Expert Review of Clinical Pharmacology, 11:8, 743-746,

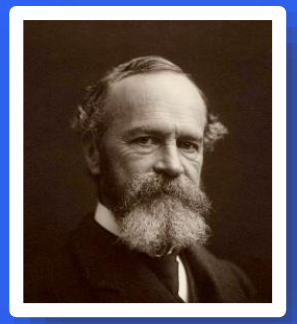
PBPK/IVIVE (+ QSP)

The Experience of Population-Based PBPK to Be Expanded to Individual Patient

Using Virtual Twins to Determine Accurate Personalized Dose



William James

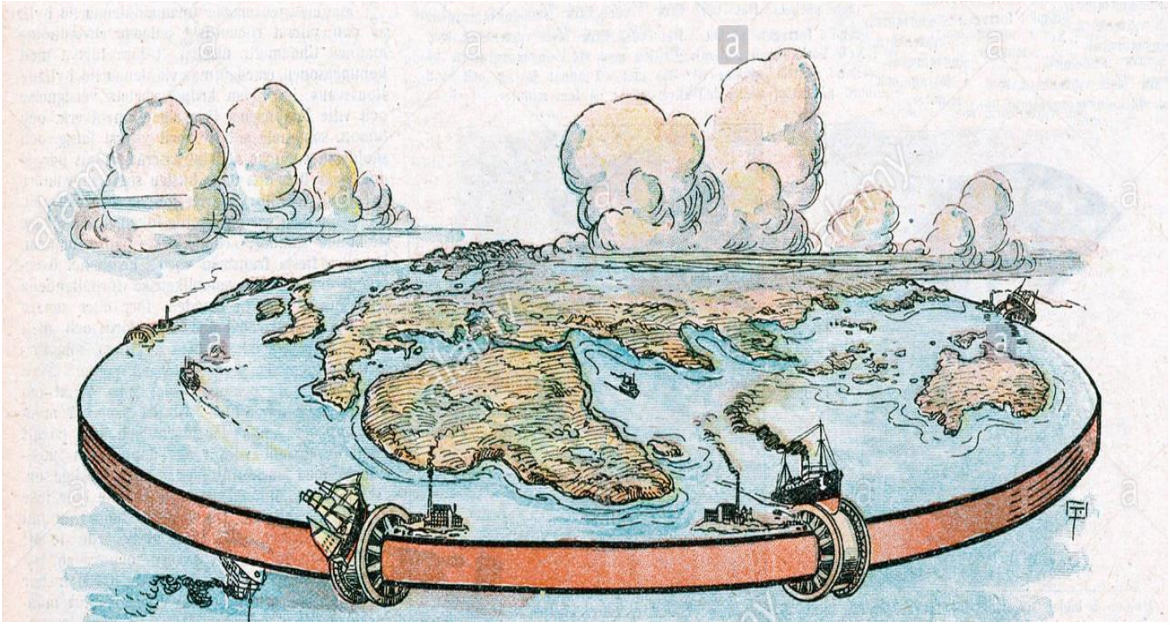


When a thing was new, people said that it was not true;

When its truth could not be denied, people said it was not important;

When its importance could not be denied, people said that it was not new!

PBPK/IVIVE Entering Uncharted Territories - 2020



JCP 2020

ACCP

Supplement Article

Physiologically Based Pharmacokinetics as a Component of Model-Informed Drug Development: Where We Were, Where We Are, and Where We Are Heading

The Journal of Clinical Pharmacology 2020, 60(S1) S12–S16

DOI: 10.1002/jcph.1654

Amin Rostami-Hodjegan, PhD, PharmD, FCP[1,2] and Stephen Toon, PhD[2]

PBPK ship sailing to Uncharted Waters: **Biopharmaceutics Space & Virtual Bioequivalence (VBE)**

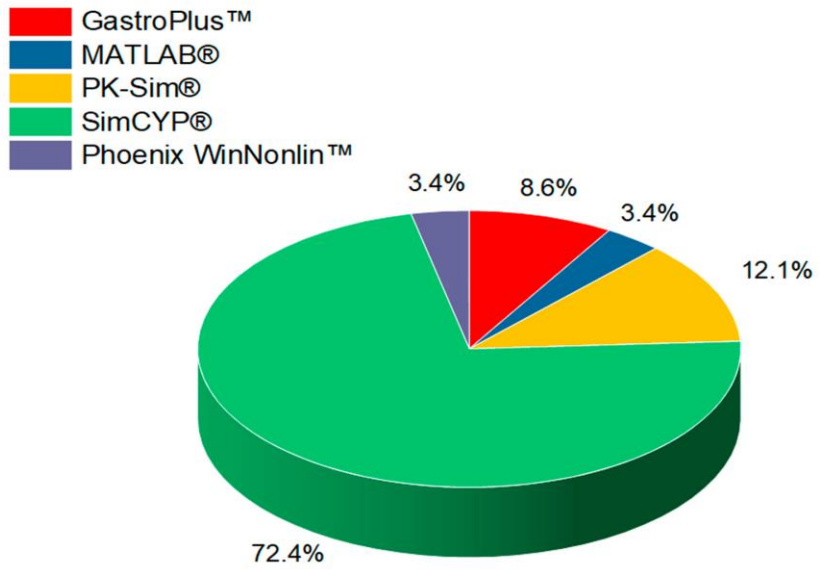
pharmaceutics

MDPI

Review

Advancements in Virtual Bioequivalence: A Systematic Review of Computational Methods and Regulatory Perspectives in the Pharmaceutical Industry

Nasser Alotaiq [1,*] and Doni Dermawan [2]



Changing Mindset & Breaking Things to Small Bits

In Search of Impossible!

THERE IS

NO

UNIQUE

Predictive Dissolution

Which Caters for 'All' Clinical Conditions

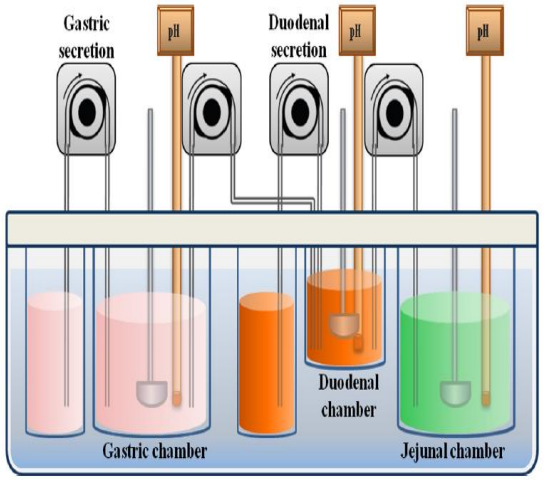
Journal of Pharmaceutical Innovation (2020) 15:296–317
https://doi.org/10.1007/s12247-019-09392-6

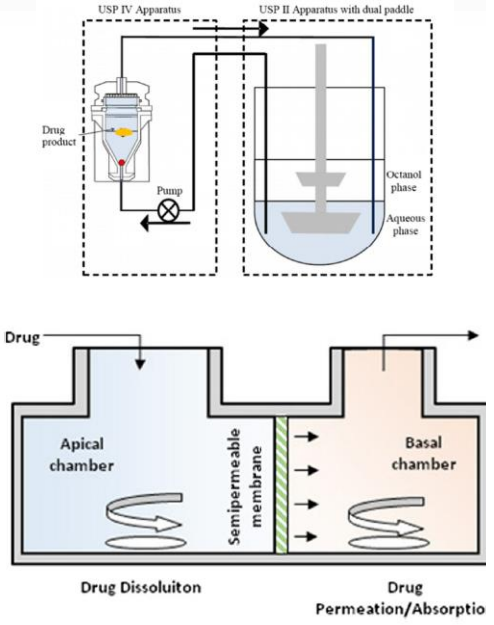
REVIEW ARTICLE

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]





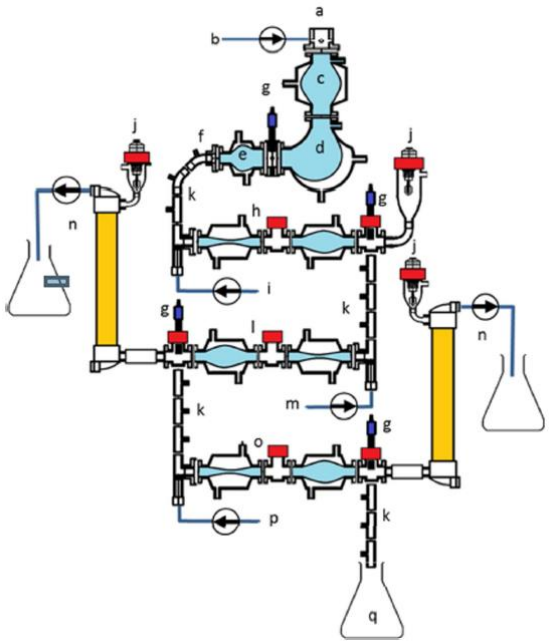


Fig. 1 Schematic of the dissolution/permeation (D/P) system

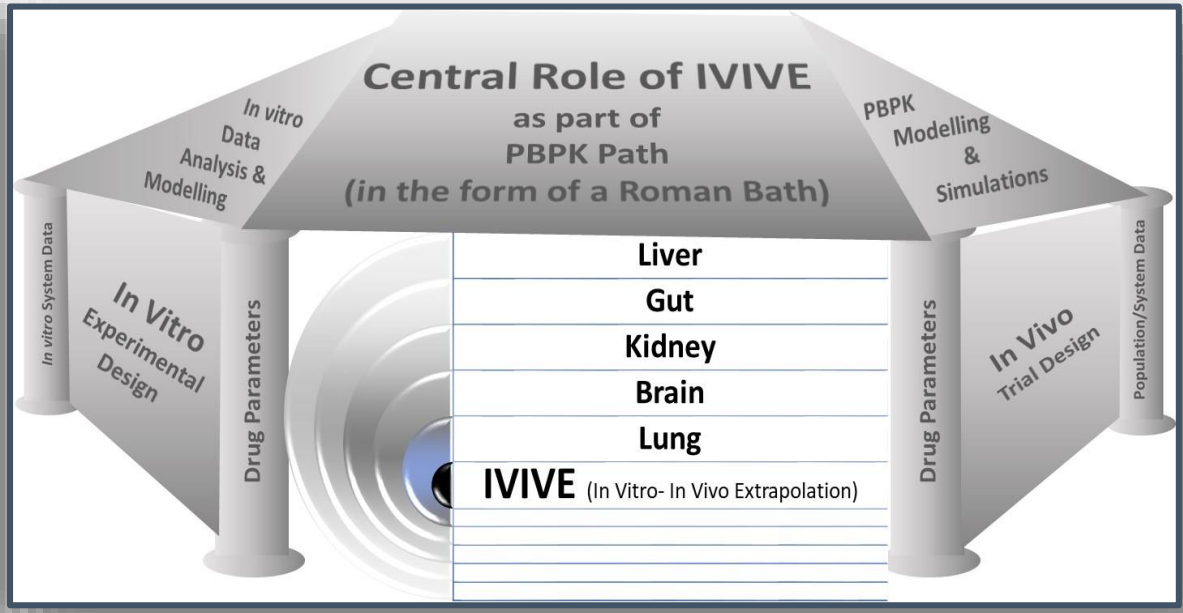
23

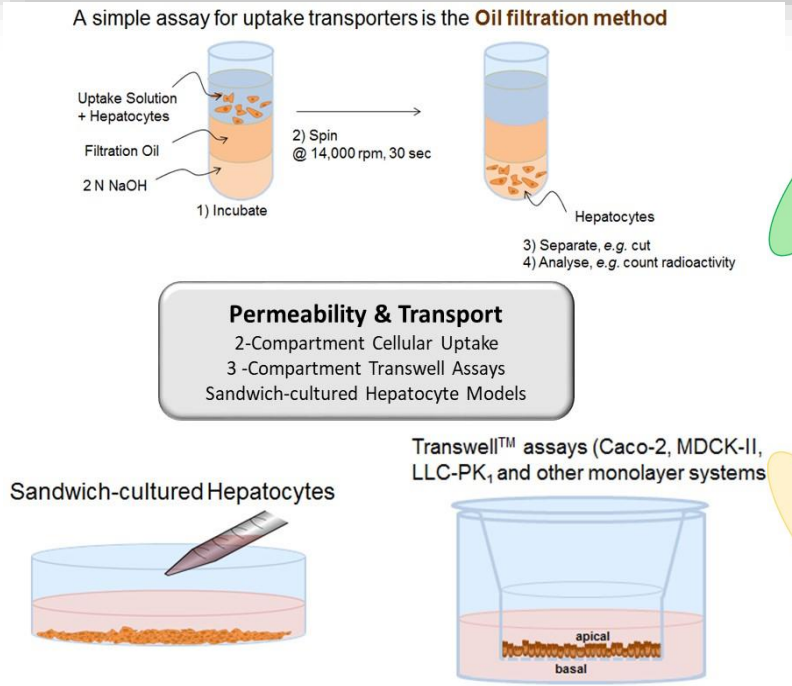
APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC AND PHARMACODYNAMIC (PBPK/PD) MODELING COMPRISING TRANSPORTERS: DELINEATING THE ROLE OF VARIOUS FACTORS IN DRUG DISPOSITION AND TOXICITY

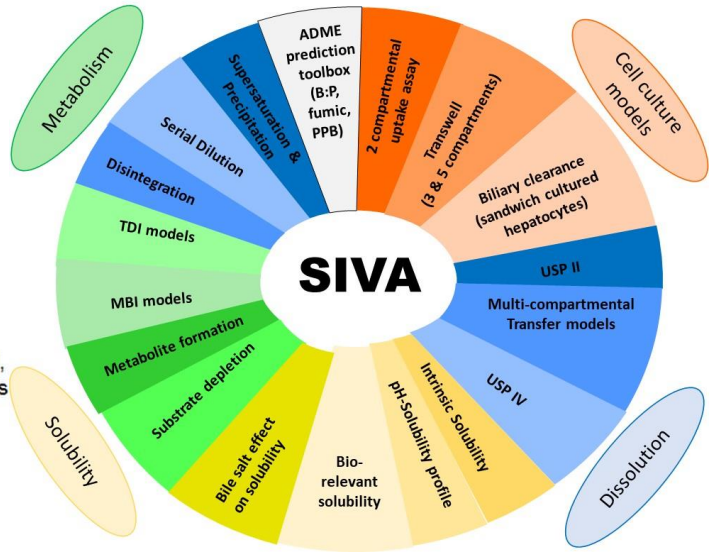
MATTHEW D. HARWOOD[1], AMIN ROSTAMI-HODJEGAN[1,2], AND SIBYLLE NEUHOFF[1]

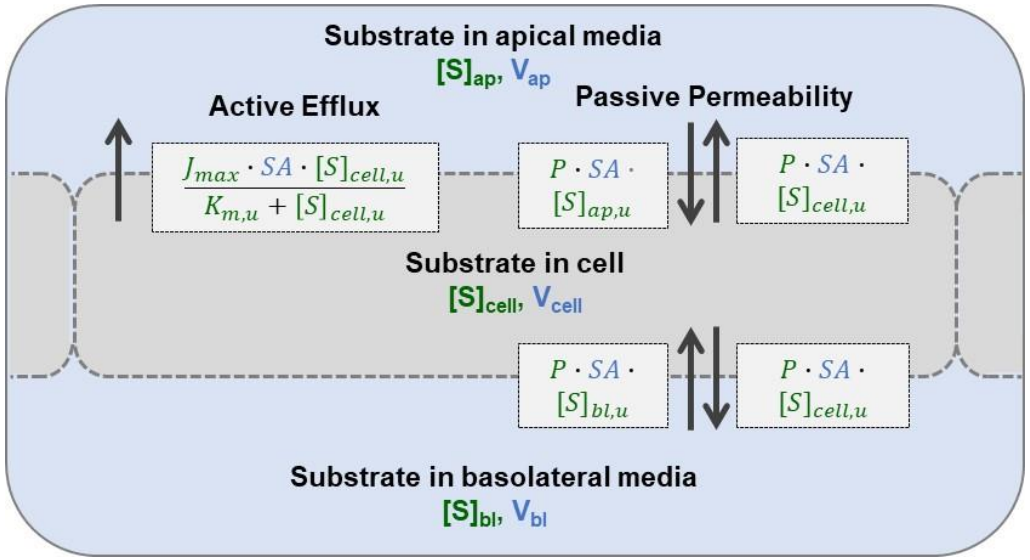
[1] *Simcyp Division, Certara UK Ltd., Sheffield, UK*

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







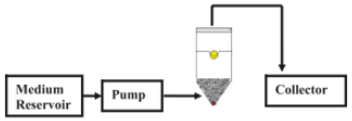


Distinguishing between the Type of Data: '*In Vitro* Set-Dependent' *vs* 'Intrinsic Parameters'

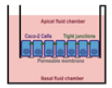
Modeling biopharmaceutic data

Solubility

Dissolution

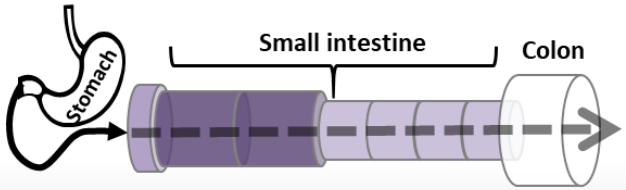


Dissolution

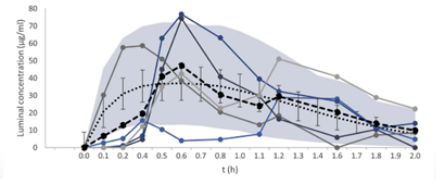


Permeability

Integrating biopharmaceutics with gastrointestinal physiology and variability



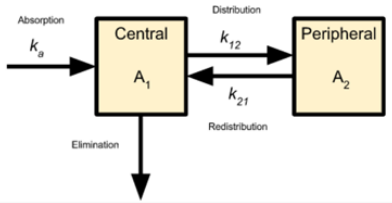
Simulating intraluminal concentrations at individual level



Assessing model performance and credibility at intraluminal level

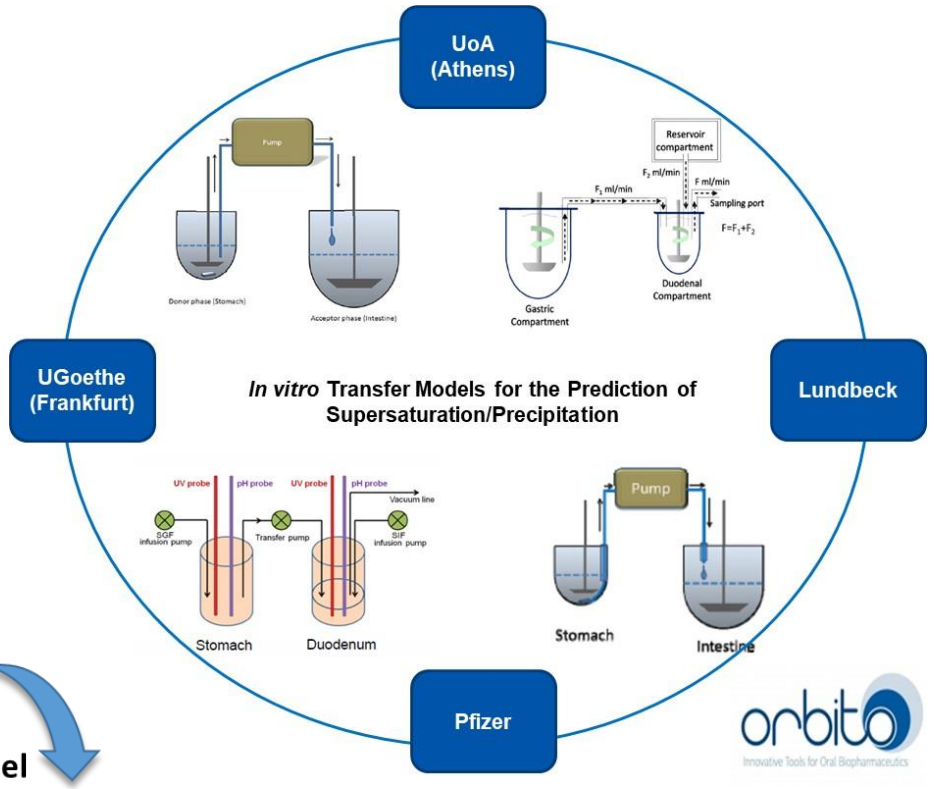
Model refinement

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

PBPK/IVIVE Linked Models: Biopharmaceutics Space

Systems Data | **Trial Design** | **API/Formulation Data**

Solid Drug Absorption

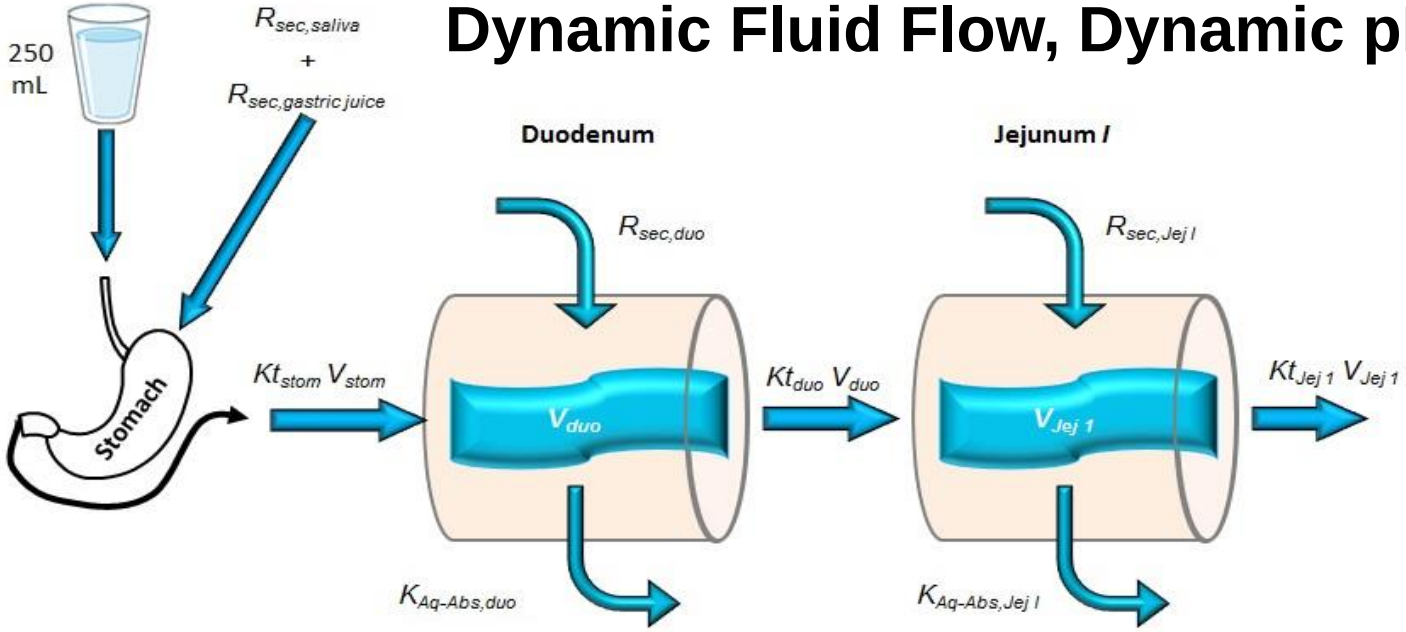
- Gastric emptying
- Intestinal motility
- pH
- Enzyme Abundance
- Disease state (Intest. Mot & Metab.)
- P-gp and other transporters
- Intestinal blood flow
- Food effects
- GI-tract fluid dynamics

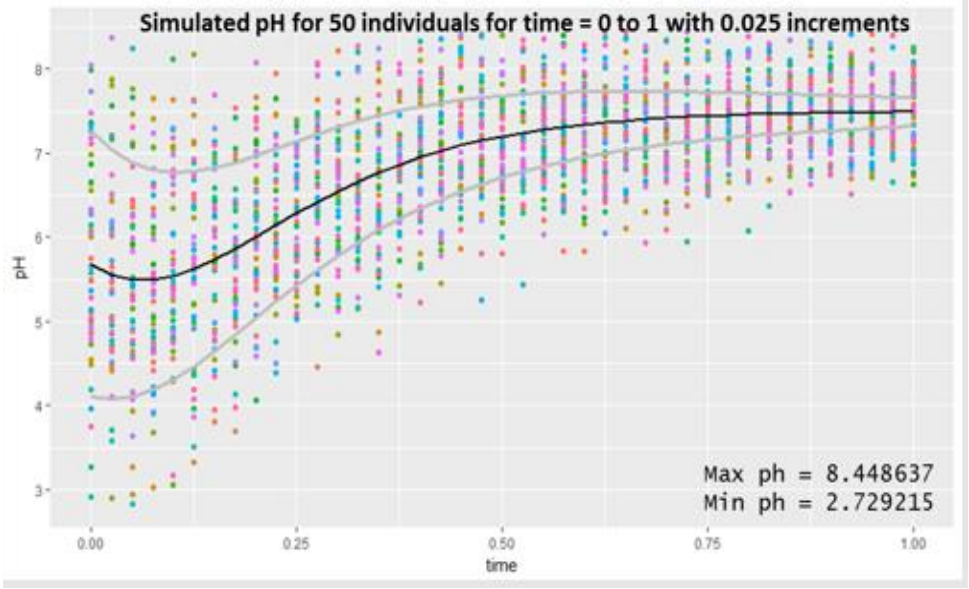
Mechanistic IVIVE & PBPK/PD

Population Variability In PK(/PD)

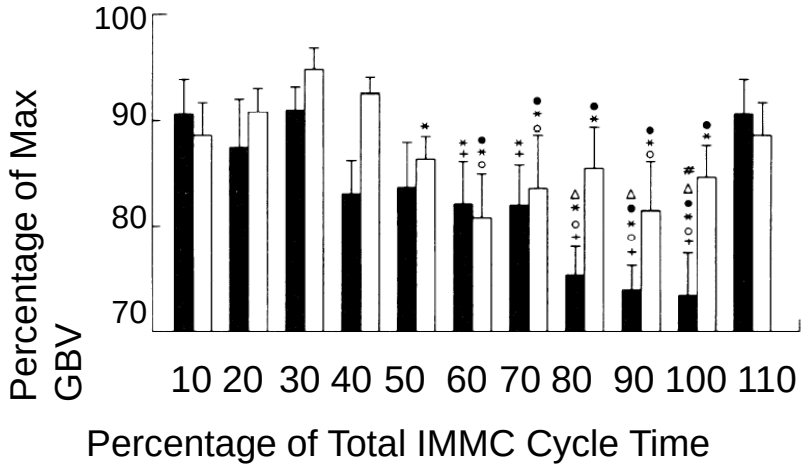
- Disintegration
- De-aggregation/Breakdown
- Release (IR, MR)
- Dissolution
- Solubility
- Precipitation
- Permeability
- Intestinal metabolism
- Intra-gut degradation

Dynamic Fluid Flow, Dynamic pH



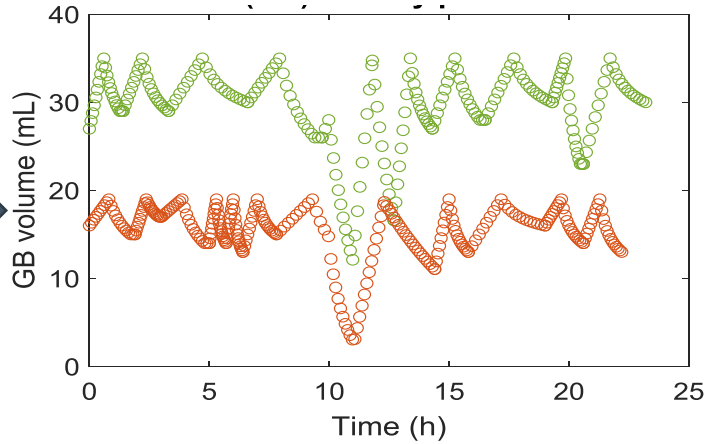


Gallbladder Volume (GBV) & IMMC Cycle



Stolk et al., 1993

Dynamic Bile



Marzio et al., 1988

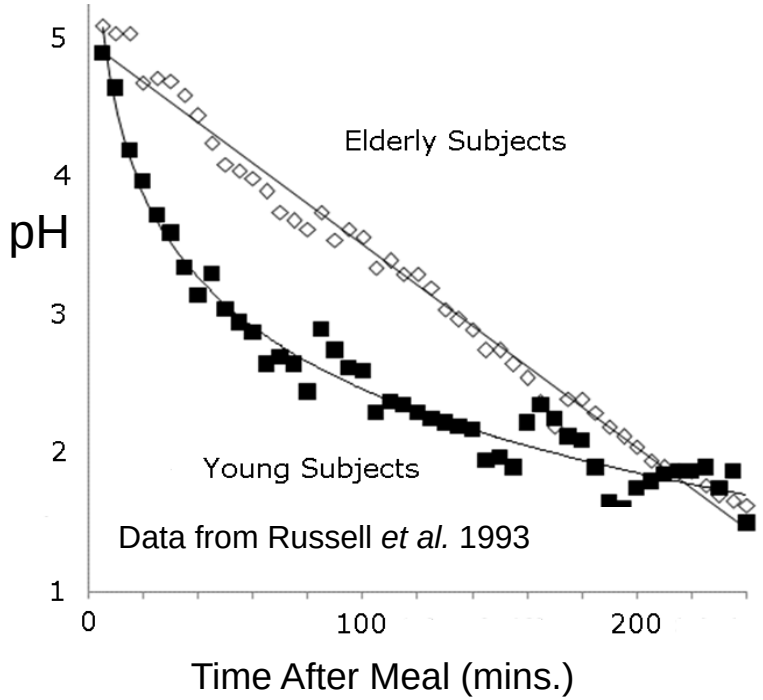
Every Attribute of Gut Lumen is

DYNAMIC & VARIABLE

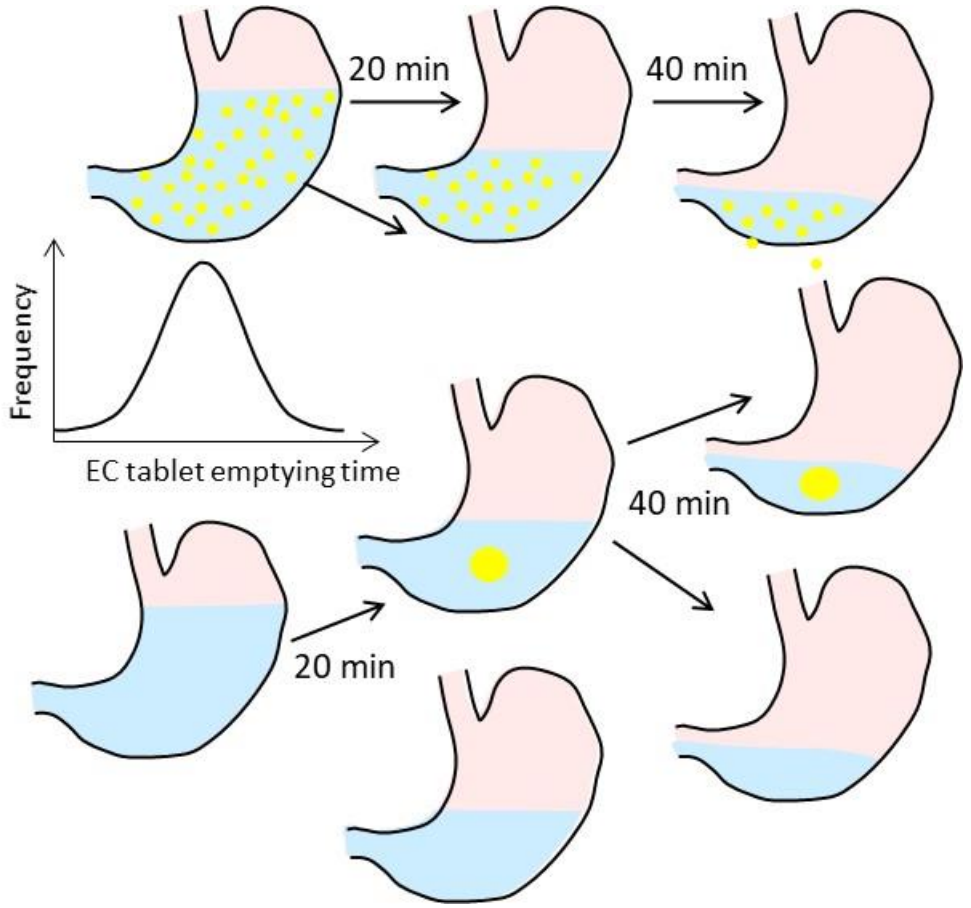
Formulation-Dependent Sensitivity to Variations in GI Tract

Population-Dependent behaviour of GI-Tract Variations

Pattern for Return of Gastric pH to Acidic Status after Food is *Age Dependent*



Enteric-Coated Granules



Enteric-Coated Tablet (ECT)

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]

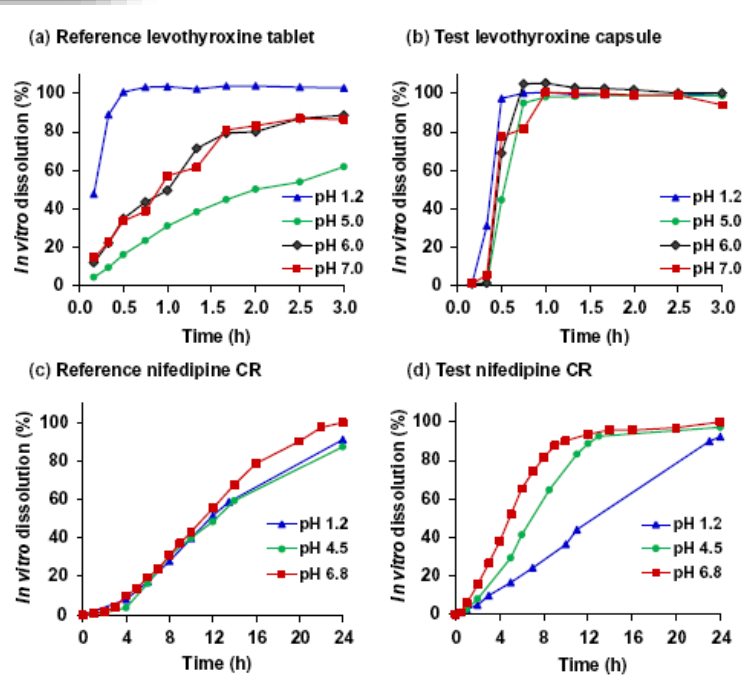
Relevance to Japanese Populations

Disparity in BE between

Healthy Volunteers and Achlorhydric Subjects

FORMULATION-DEPENDENT

(less pronounced for levothyroxine formulations as compared to nifedipine CR)



Relevance to Afro-American Populations

AJKD

Editorial

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

Dirk R.J. Kuypers

Clues were there:

PBPK/Gradient of CYP 3A in GI-Tract/CR Formulation

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

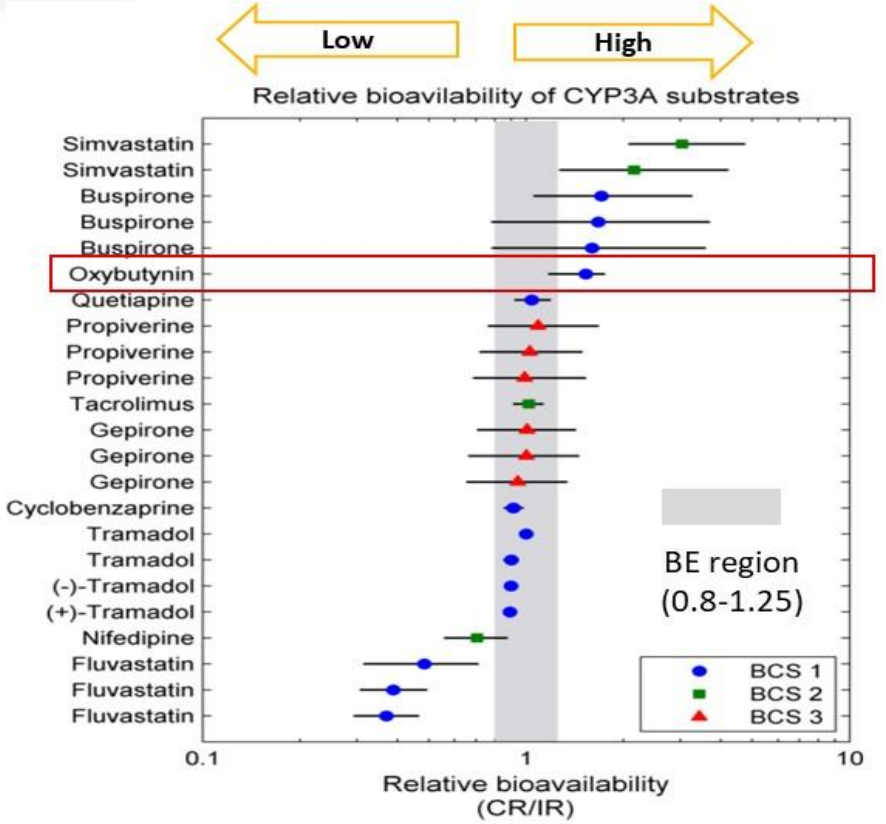
Contents lists available at ScienceDirect

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,*]

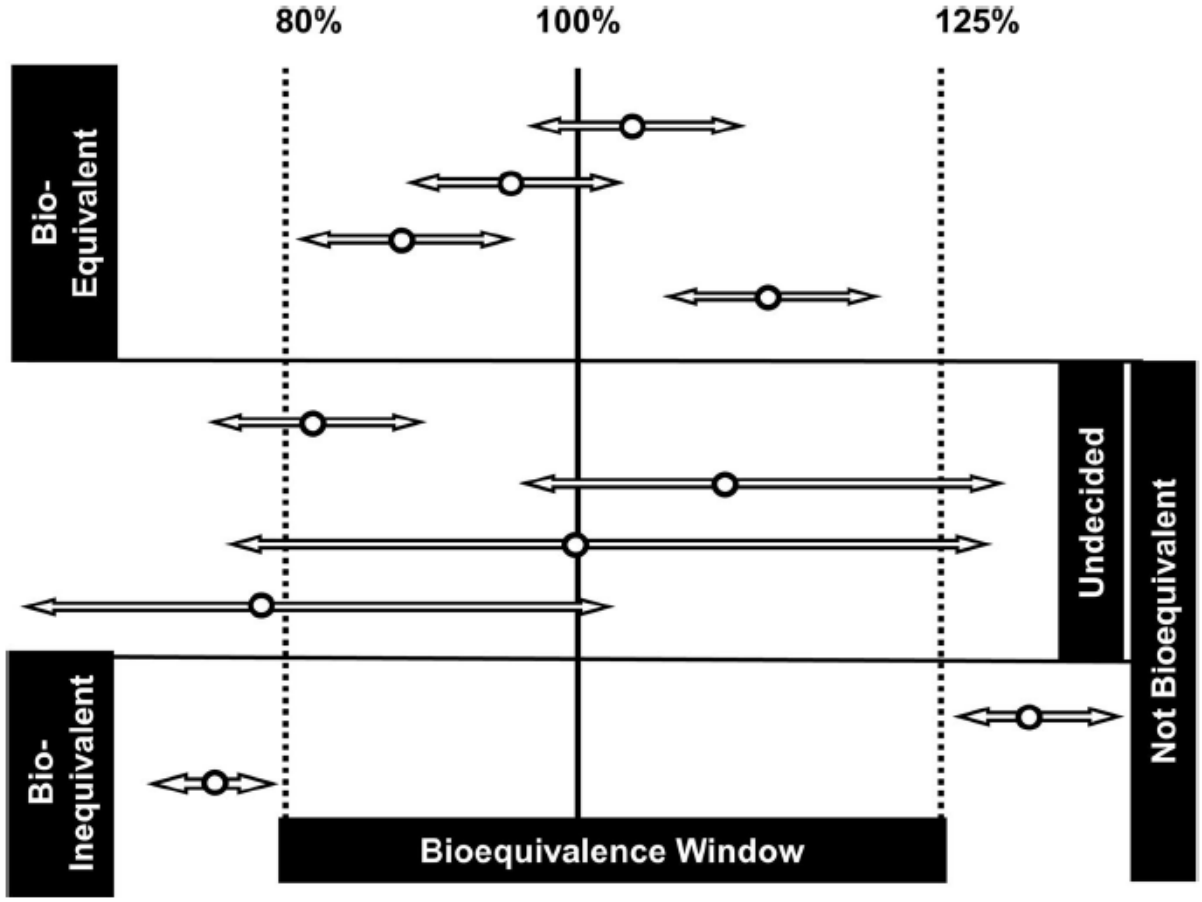


Why Perform Bioequivalence Studies?

- Generic product
- Development to Market formulation
- Conventional tablet to Slow-release

How to Do Bioequivalence Studies?

- Must allow formulation effects to be distinguished
- Cross-over design is first choice
- Random allocation of subjects



The AAPS Journal (2022) 24:21

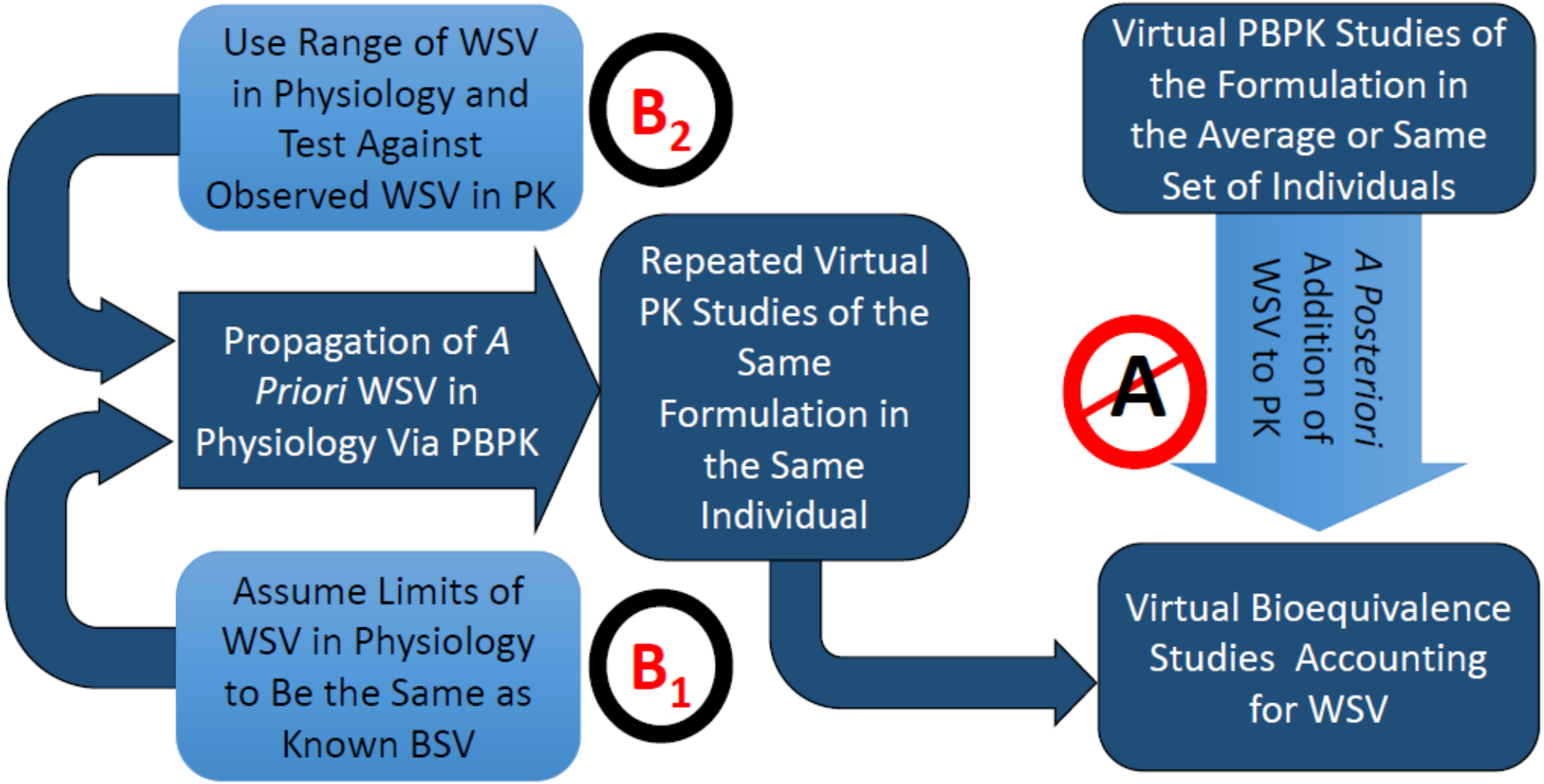
What to analyse from the data?

- AUC, C_{max}, t_{Max}

Proof of Concept in Assignment of Within-Subject Variability During Virtual Bioequivalence Studies: Propagation of Intra-Subject Variation in Gastrointestinal Physiology Using Physiologically Based Pharmacokinetic Modeling

Margareta Bego,[1] Nikunjkumar Patel, Rodrigo Cristofoletti,[4] Amin Rostami-Hodjegan

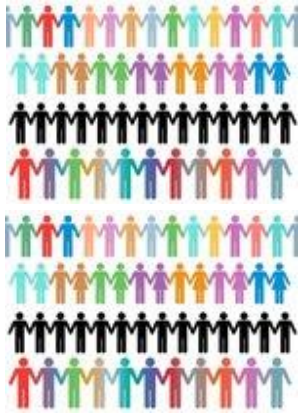
Workflows of VBE Studies Accounting for WSV

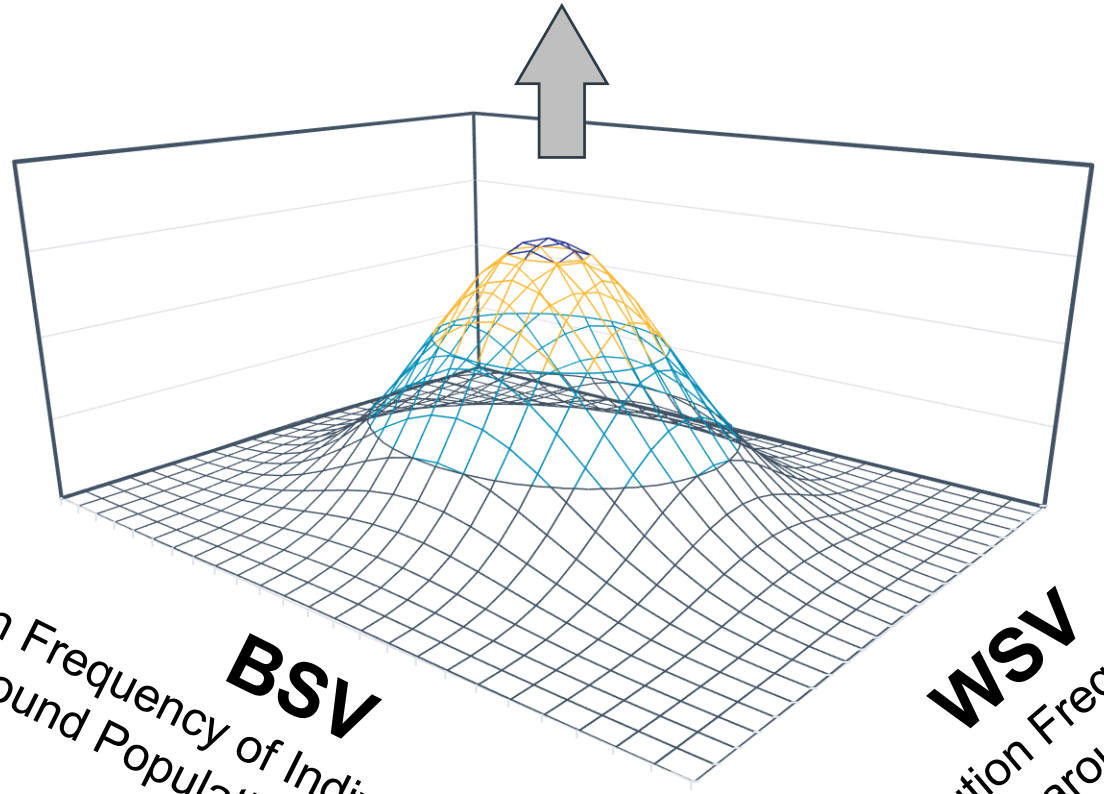


Bego *et al.* 2022,AAPS J

Apparent BSV

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



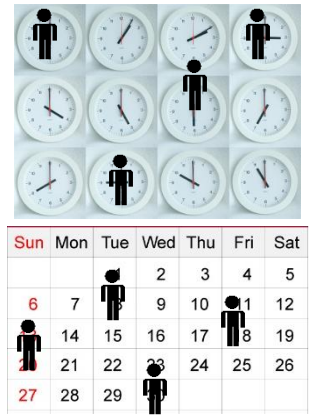


BSV

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)

Focusing on Lessons Learnt

Retrospective **Prospective**

Past **Present** **Future**

(1) The field is not static and developments are happening all the time,

(2) If the MMF becomes part of submission, the clinical applications will follow,

(3) Patient characterisations (beyond genetics) is required for individualisation,

(4) Biopharmaceutics applications are increasing but mindset needs to change,

(5) Like DMPK, intrinsic information are needed to feed PBPK/IVIVE models,

(6) For VBE, information on WSV is a key unknown regarding physiology.

PBPKAVIVE
Feeds into Virtual Trials

For Such Virtual Trials, We Cannot Afford to Oversimplify the *In Vitro* Studies, Associated Data Analysis, or the Models That They Feed into.

Q & A

Henry Mencken

For every complex problem, there's a solution that Is simple, clear, and

Wrong!