aaps PharmSci 360
OCT 16-19 2022

Lost in Translation? Predict first-in-human PK with Simcyp Discovery

18th October 2022

Hannah M. Jones, Certara

Session Description and Objectives

This session will focus on:

- Basic PBPK concepts – model background, model inputs and modelling strategy
- Paridigms for applying PBPK modelling to support FIH dose selection
- Other potential applications for PBPK in the discovery and pre-clinical phases of drug development

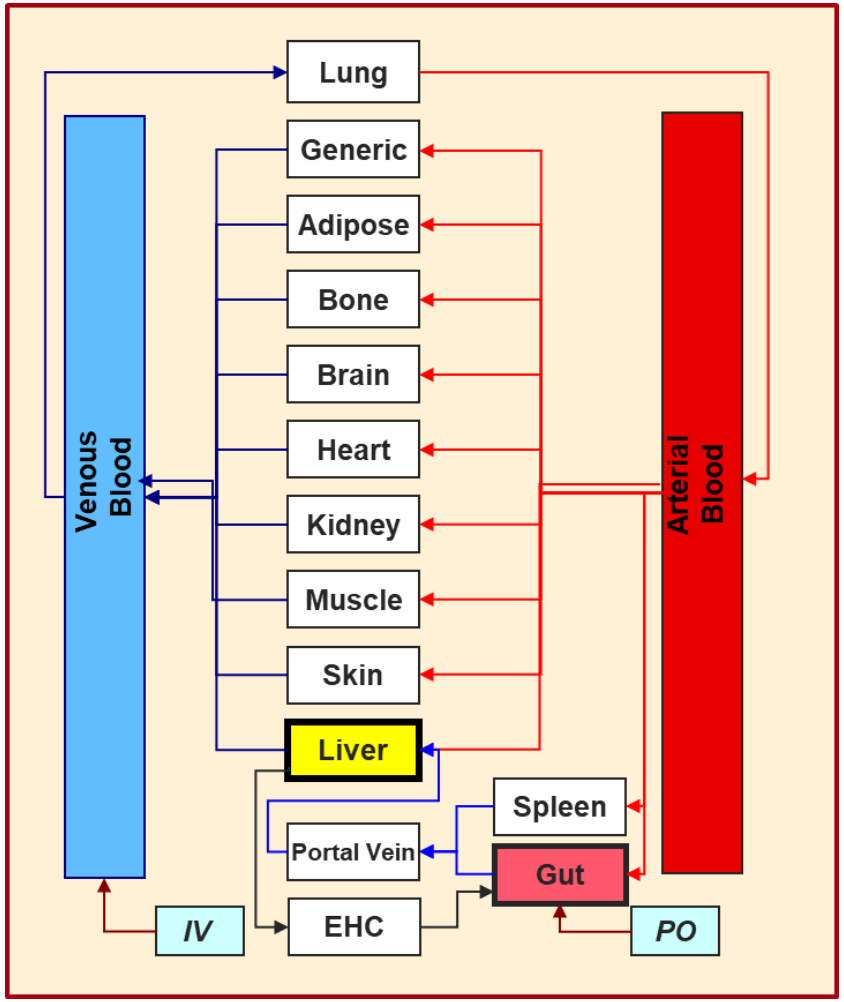
Biography: Hannah M. Jones, Ph.D.

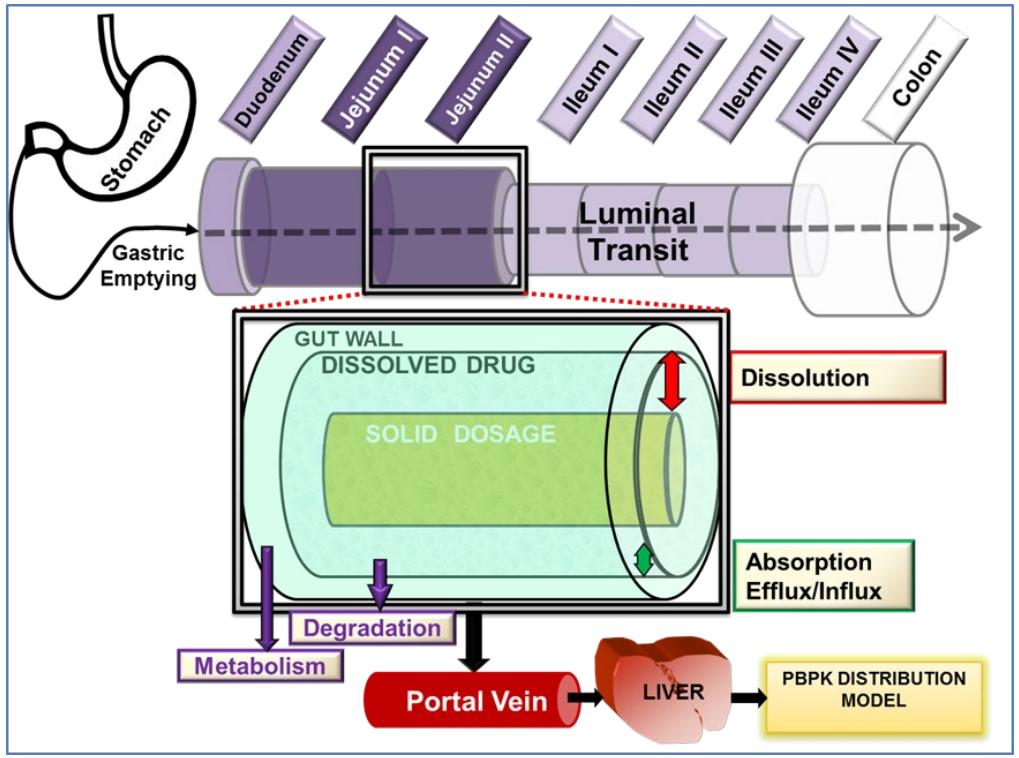
- Scientific leader in modelling and simulation
- Head of PBPK Consulting Services at Certara
- 20+ years in global pharmaceutical organizations (including Pfizer & Roche)
- Over 60 publications in PBPK/PKPD modelling and other DMPK related topics
- Considerable experience influencing drug research and development programs through modelling and simulation

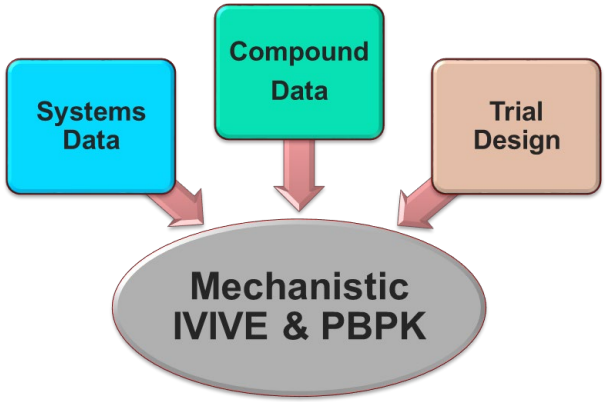
Sr. Vice President and Head of PBPK Consulting Services at Certara

hannah.jones@certara.com

What is Whole body PBPK modelling?

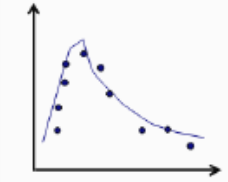






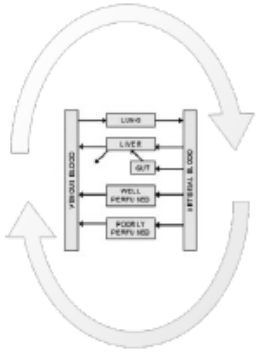
PBPK application in drug discovery and development

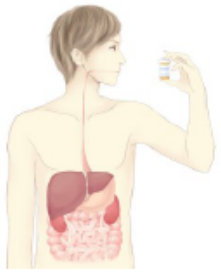
Discovery

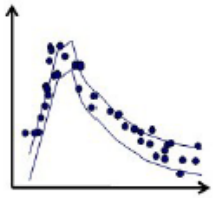


Early risk assessment,
Early first in human dose projection,
Toxicokinetic dose projection,
Early formulation assessment

Early Development



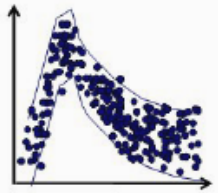




'Learn and confirm' through data integration

First in human, single/multiple ascending dose exposure or efficacy modeling,
Drug-Drug interaction, Food effect,
Formulation/Absorption modeling
Healthy subjects & patients

Late Development



Phase I-IV trials
Patient trials,
Special populations,
Label requirements

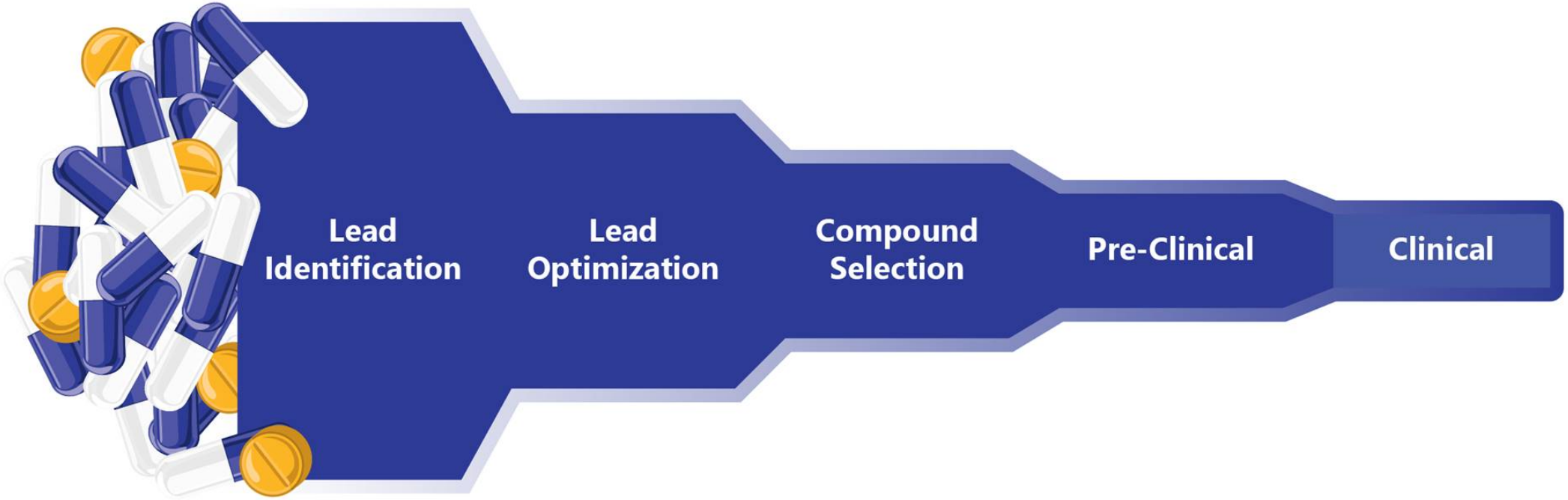
Continuous Model Refinement & Verification

Simulating Virtual Patients and Waiving Clinical Studies

More than 300 label claims for 90+ novel drugs using the Simcyp Simulator

ONCOLOGY	Agios	Tibsovo *(ivosidenib)*	Genentech	Alecensa *(alectinib)*	Novartis	Vijoice *(alpelisib)*
	Amgen	Blincyto *(blinatumomab)*	Genentech	Cotellic *(cobimetinib)*	Novartis	Rydapt *(midostaurin)*
	Amgen	Lumakras *(sotorasib)*	Genentech	Polivy *(polatuzumab vedotin-piiq)*	Novartis	Tabrecta *(capmatinib)*
	Ariad	Alunbrig *(brigatinib)*	Genentech	Rozlytrek *(entrectinib)*	Novartis	Zykadia *(ceritinib)*
	Ariad (Takeda)	Iclusig *(ponatinib)*	Incyte	Pemazyre *(pemigatinib)*	Novartis	Jakavi *(ruxolitinib)*
	AstraZeneca	Calquence *(acalabrutinib)*	Janssen	Balversa *(erdafitinib)*	Pfizer	Bosulif *(bosutinib)*
	AstraZeneca	Lynparza *(olaparib)*	Janssen	Erleada *(apalutamide)*	Pfizer	Lorbrena *(lorlatinib)*
	AstraZeneca	Tagrisso *(osimertinib)*	Lilly	Retevmo *(selpercatinib)*	Pharmacyclics	Imbruvica *(ibrutinib)*
	Beigene	Brukinsa *(zanubrutinib)*	Lilly	Verzenio *(abemaciclib)*	Sanofi	Jevtana *(cabazitaxel)*
	BluePrint Medicines	Ayvakit *(avapritinib)*	Loxo Oncology	Vitrakvi *(larotrectinib)*	Seattle Genetics	Tukysa *(tucatinib)*
	Celgene	Inrebic *(fedratinib hydrochloride)*	Novartis	Farydak *(panobinostat)*	Spectrum	Beleodaq *(belinostat)*
	Daiichi Sankyo	Turalio *(pexidartinib)*	Novartis	Kisqali *(ribociclib succinate)*	Takeda	Exkivity *(mobocertinib)*
	Eisai	Lenvima *(lenvatinib)*	Novartis	Scemblix *(asciminib)*	Verastem	Copiktra *(duvelisib)*
	EMD Serono	Tepmetko *(tepotinib hydrochloride)*	Novartis	Odomzo *(sonidegib)*		
RARE DISEASE	AkaRx (Eisai)	Doptelet *(avatrombopag maleate)*	Intercept	Ocaliva *(obeticholic acid)*	PTC Therapeutics	Emflaza *(deflazacort)*
	AstraZeneca	Koselugo *(selumetinib)*	Kadmon	Rezurock *(belumosudil)*	Sanofi Genzyme	Cerdelga *(eliglustat tartrate)*
	Aurinia	Lupkynis *(voclosporin)*	Merck	Welireg *(belzutifan)*	Vertex	Symdeko *(tezacaftor/ivacaftor)*
	Genentech	Enspryng *(satralizumab)*	Mirum	Livmarli *(maralixibat)*	Vertex	Trikafta *(elexacaftor/ivacaftor/tezacaftor)*
	Genentech	Evrysdi *(risdiplam)*	Mitsubishi Tanabe	Dysval *(Valbenazyne)*		
	Global Blood Therapeutics	Oxbryta *(voxelotor)*	Novartis	Isturisa *(osilodrostat)*		
CENTRAL NERVOUS SYSTEM	AbbVie	Rinvoq *(upadacitinib)*	Eisai	Dayvigo *(lemborexant)*	Kyowa Kirin	Nourianz *(istradefylline)*
	AbbVie	Qulipta *(atogepant)*	GW Research	Epidiolex *(cannabidiol)*	Lilly	Reyvow *(lasmiditan succinate)*
	Alkermes	Aristada *(aripiprazole lauroxil)*	Idorsia	Quviviq *(daridorexant)*	Novartis	Mayzent *(siponimod fumaric acid)*
	Alkermes	Lybalvi *(olanzapine/samidorphan)*	Janssen	Ponvory *(ponesimod)*	UCB	Briviact *(brivaracetam)*
INFECTIOUS DISEASE	Gilead	Veklury *(remdesivir)*	Merck	Prevymis *(letermovir)*	Tibotec	Edurant *(rilpivirine)*
	Janssen	Olysio *(simeprevir)*	Nabriva	Xenleta *(lefamulin acetate)*	ViiV	Cabenuva Kit *(cabotegravir, rilpivirine)*
	Merck	Pifeltro *(doravirine)*	Novartis	Egaten *(triclabendazole)*		
GASTROENTEROLOGY	AstraZeneca	Movantik *(naloxegol)*	Phathom	Voquezna Triple Pak	Shire	Motegrity *(prucalopride)*
	Helsinn	Akynzeo *(fosnetupitant/palonosetron)*	Shionogi	Symproic *(naldemedine)*		
CARDIOVASCULAR	Actelion (J & J)	Opsumit *(macitentan)*	BMS	Camzyos *(mavacamten)*	Pfizer	Revatio *(sildenafil)*
	Bayer (and Merck)	Verquvo *(vericiguat)*	Johnson & Johnson	Xarelto *(rivaroxaban)*		
OTHER	AbbVie	Orilissa *(elagolix)*	Janssen	Invokana *(canagliflozin)*	Merck	Steglatro *(ertugliflozin)*
	Agios	Pyrukynd *(mitapivat)*	Lilly	Olumiant *(baricitinib)*	Peloton/Merck	Welireg *(belzutifan)*
	Galderma	Aklief *(trifarotene)*	Lilly	Mounjaro *(tirzepadide)*	Takeda	Livtencity *(maribavir)*

PBPK Applications and Benefits in Discovery



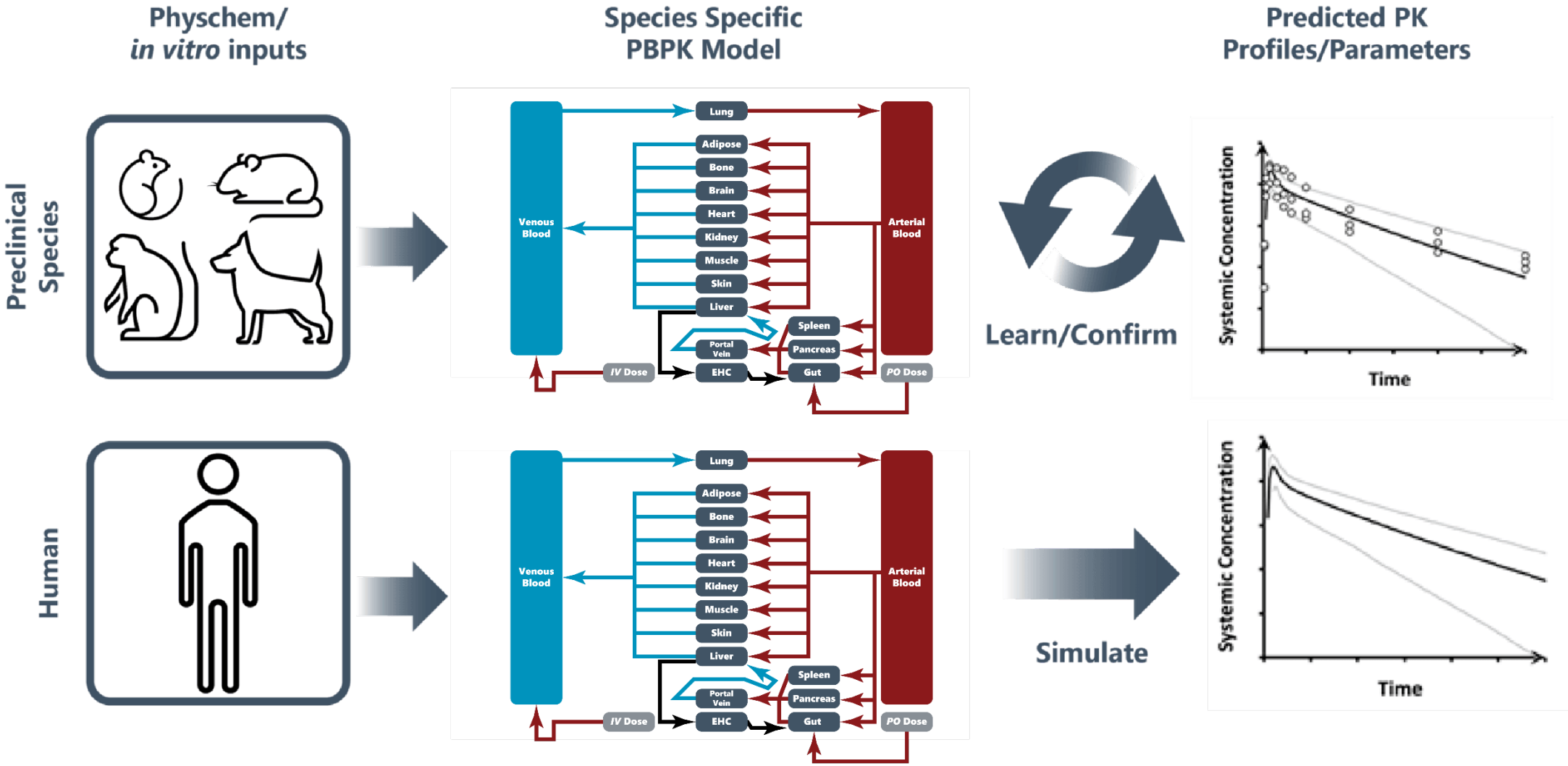
Defining lab objectives to achieve TPP

Early PK, PD and FIH dose predictions
DDI risk assessment
Early formulation screening

Prediction of exposure in tox studies

TPP = target product profile; PK = pharmacokinetics; PD = pharmacodynamics; FIH = first-in-human; DDI = drug-drug interactions

PBPK Modeling Strategy for FIH simulations



Typical PBPK Model Input Parameters

- Physchem information e.g. MW, LogP, pKa
- Plasma protein binding (fu), Blood:Plasma ratio (BP)
- In vitro CLint data / In vivo CL
- Passive permeability e.g. MDCK, Caco-2
- Aqueous solubility, biorelevant solubility e.g. FaSSIF/FeSSIF/FaSSGF
- Target exposure /dosing regimen / formulation required in human
- In vivo PK data for verification

- Inhibition Parameters for static DDI calculations (if applicable)

New PBPK tool – Simcyp Discovery

New PBPK simulator from Simcyp for discovery and translational scientists

- *Derived from the gold-standard Simcyp Simulator*
- *Species -> mouse, rat, dog, monkey and human*
- *Population info -> demographics, liver / GI tract, tissue flows, volumes and composition*
- *Compound info -> physchem, protein binding, solubility, permeability, clearance, transporters, PD*
- *Allows PK prediction across species*
- *Static DDI calculator for early DDI risk assessment*

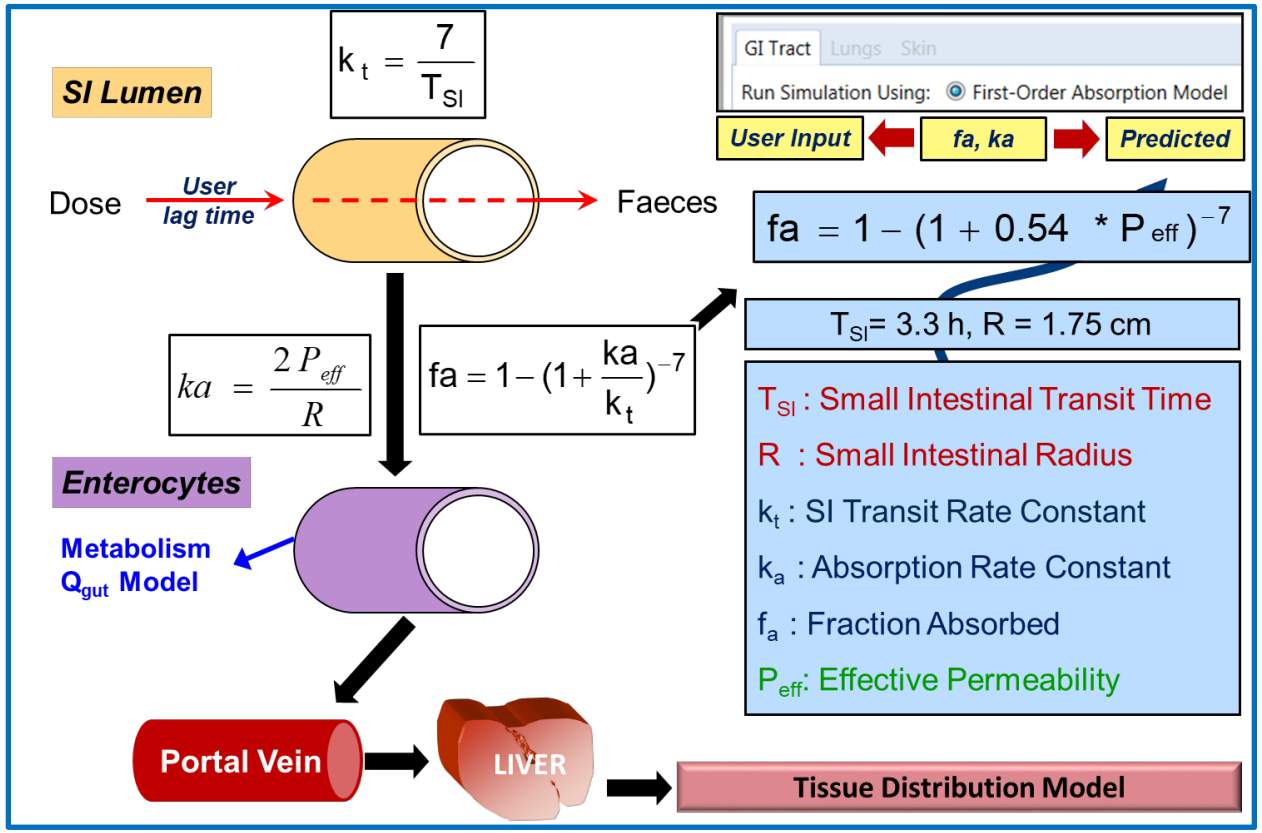
CERTARA®

Simcyp™ Discovery

First Order and ADAM Models Available

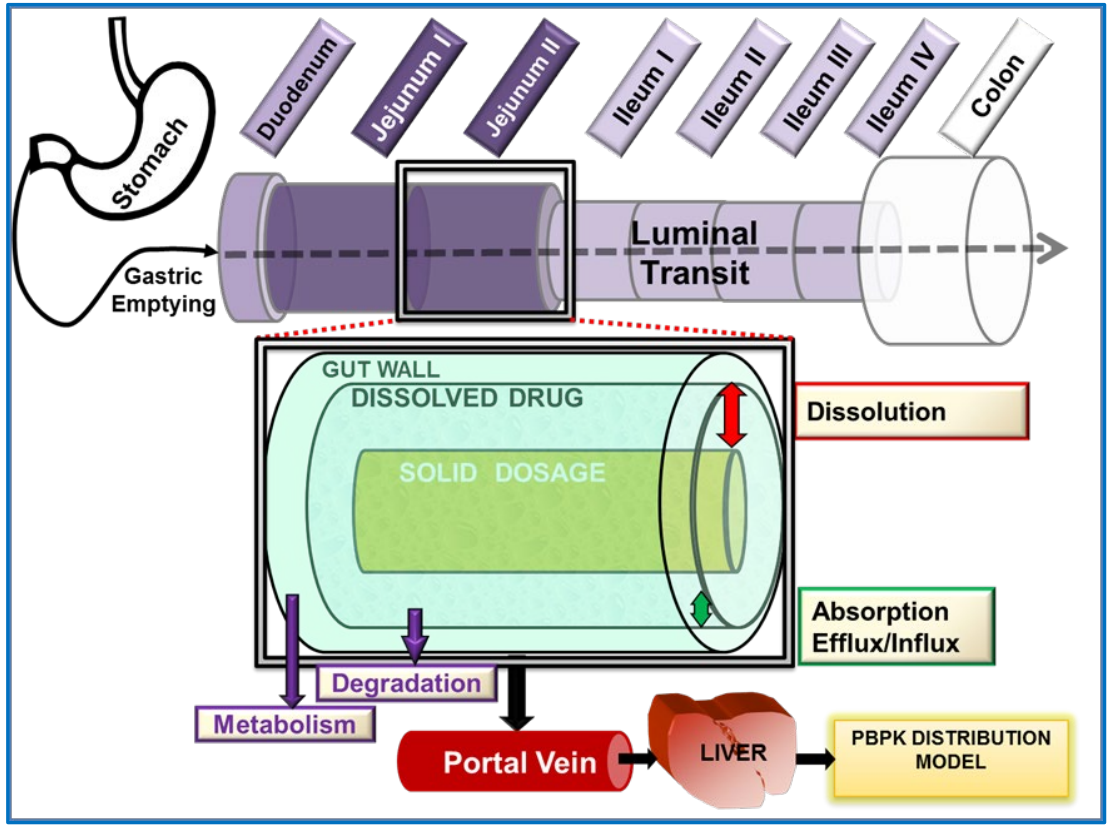
First order absorption model

For straightforward /"middle-out" modelling



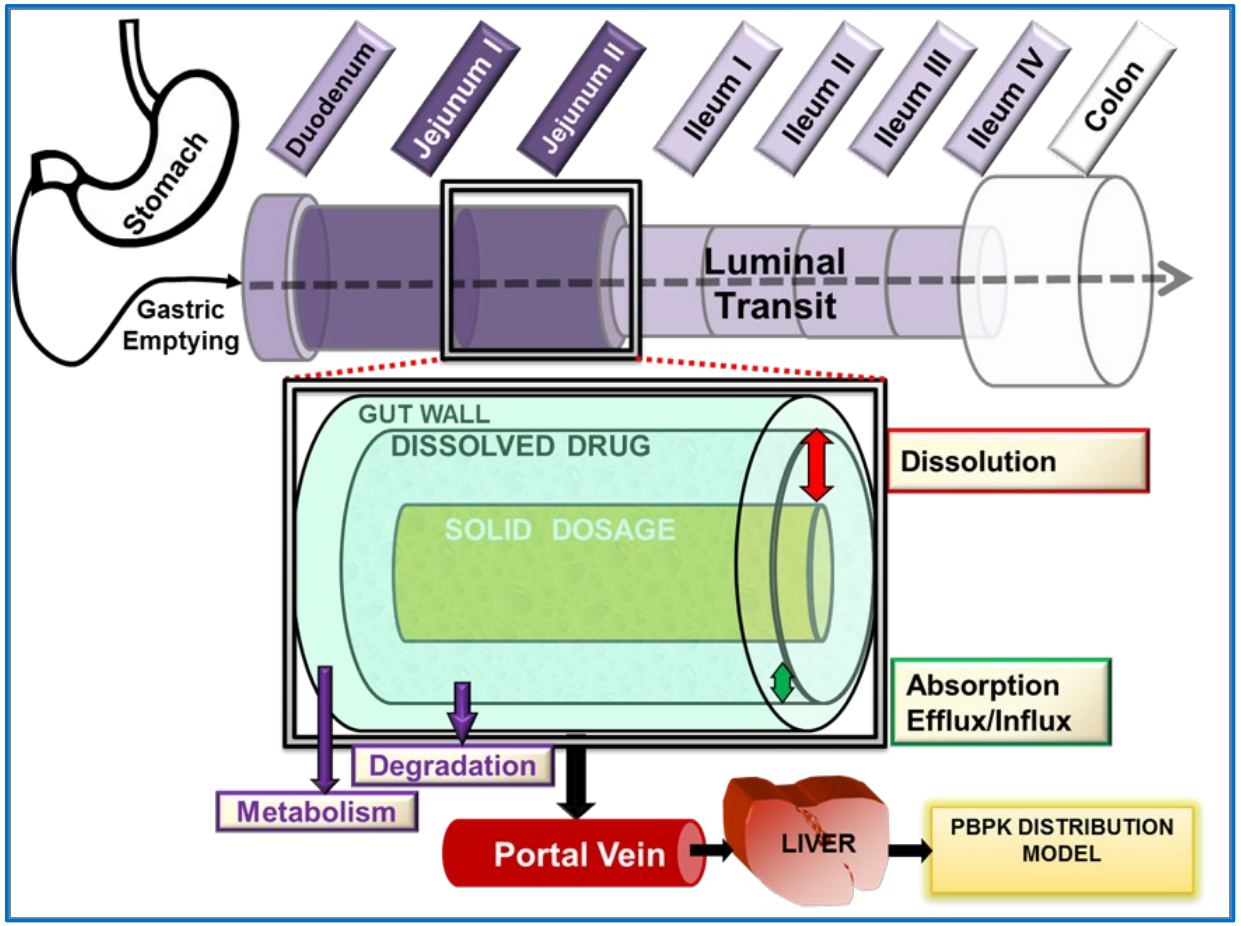
ADAM (advanced dissolution absorption and metabolism) model

For more complex /"bottom up" modelling



Prediction of Absorption using the ADAM model

ADAM (Advanced Dissolution Absorption and Metabolism) Model



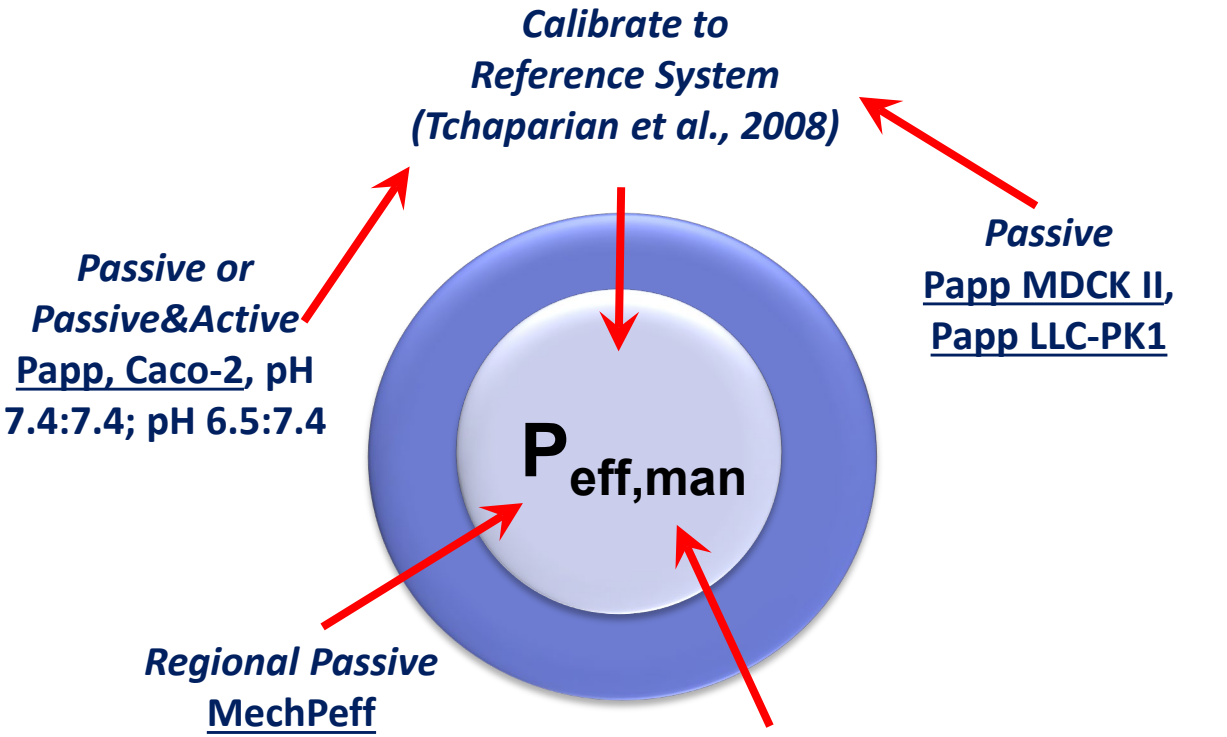
Key input parameters include solubility, permeability and particle size

Model predicts how the drug goes in and out of solution as it goes through the GIT and once in solution gets absorbed as a function of the permeability

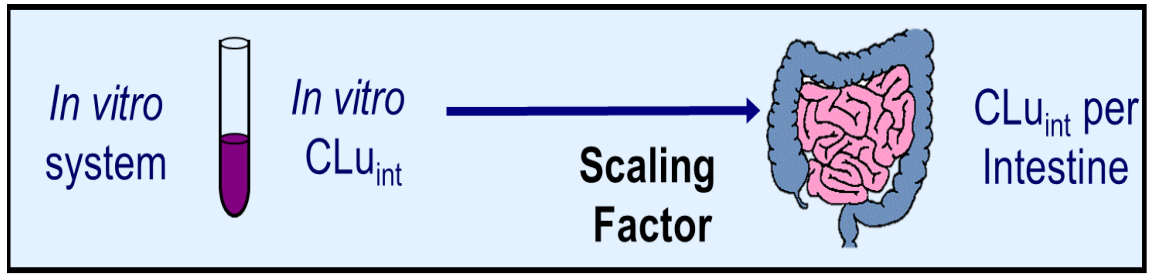
Transporter effects can also be incorporated

Prediction of Permeability and Intestinal Metabolism

Permeability (Peff) prediction



Intestinal CLint prediction



IM	$\frac{\mu L.min^{-1}}{mg\ protein}$	X	IMPPI	Direct Scaling approaches
IS	$\frac{\mu L.min^{-1}}{g\ intestine}$	X	IW	
LM	$\frac{\mu L.min^{-1}}{mg\ protein} \times \frac{Enz\ abundance_{int}}{Enz\ abundance_{liv}}$	X	MPPI	Absolute Enzyme abundance Scaling approaches
rCYP	$\frac{\mu L.min^{-1}}{pmol\ enzyme} \times \frac{pmol\ enzyme}{mg\ mic\ protein}$			

Different ADAM Formulation Options

1. Solution → API in solution at all times

2. Solution with Precipitation → API dosed in solution

3. Suspension → Particles and pre-dissolved API

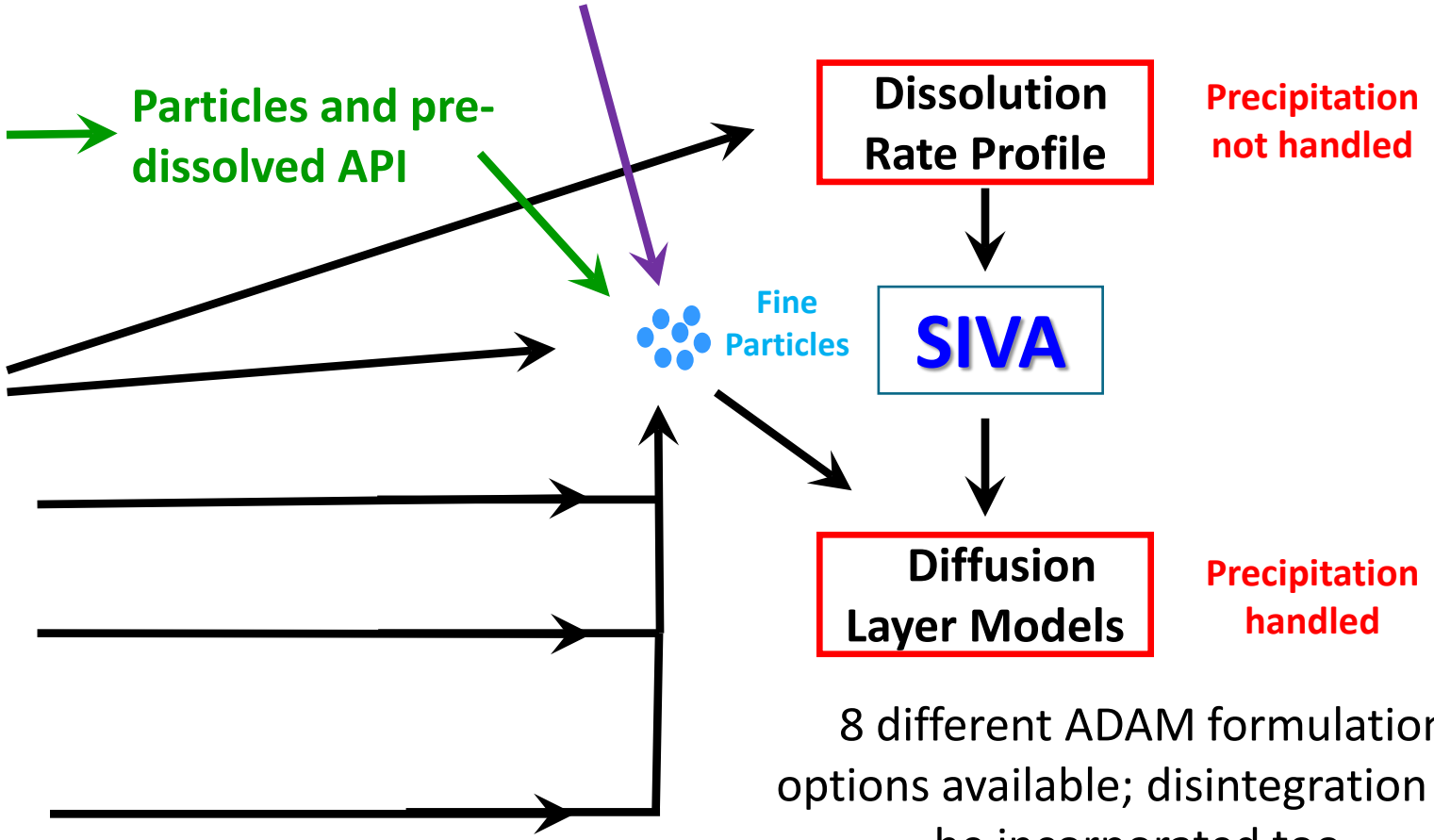
4. Solid Formulations

a. Immediate Release (IR)

b. Enteric- Coated Granules

c. Enteric-Coated Tablet

d. Modified / Controlled Release (MR/CR)



Dissolution Rate Profile → SIVA → Diffusion Layer Models

Precipitation not handled

Precipitation handled

8 different ADAM formulation options available; disintegration can be incorporated too.

Drug Distribution Models – Minimal PBPK

- (●) Minimal PBPK Model
- ( ) Full PBPK
- ( ) Compartmental

$$V_{ss} = V_p + V_e \times E:P + \sum_t V_t \times P_{t:p}$$

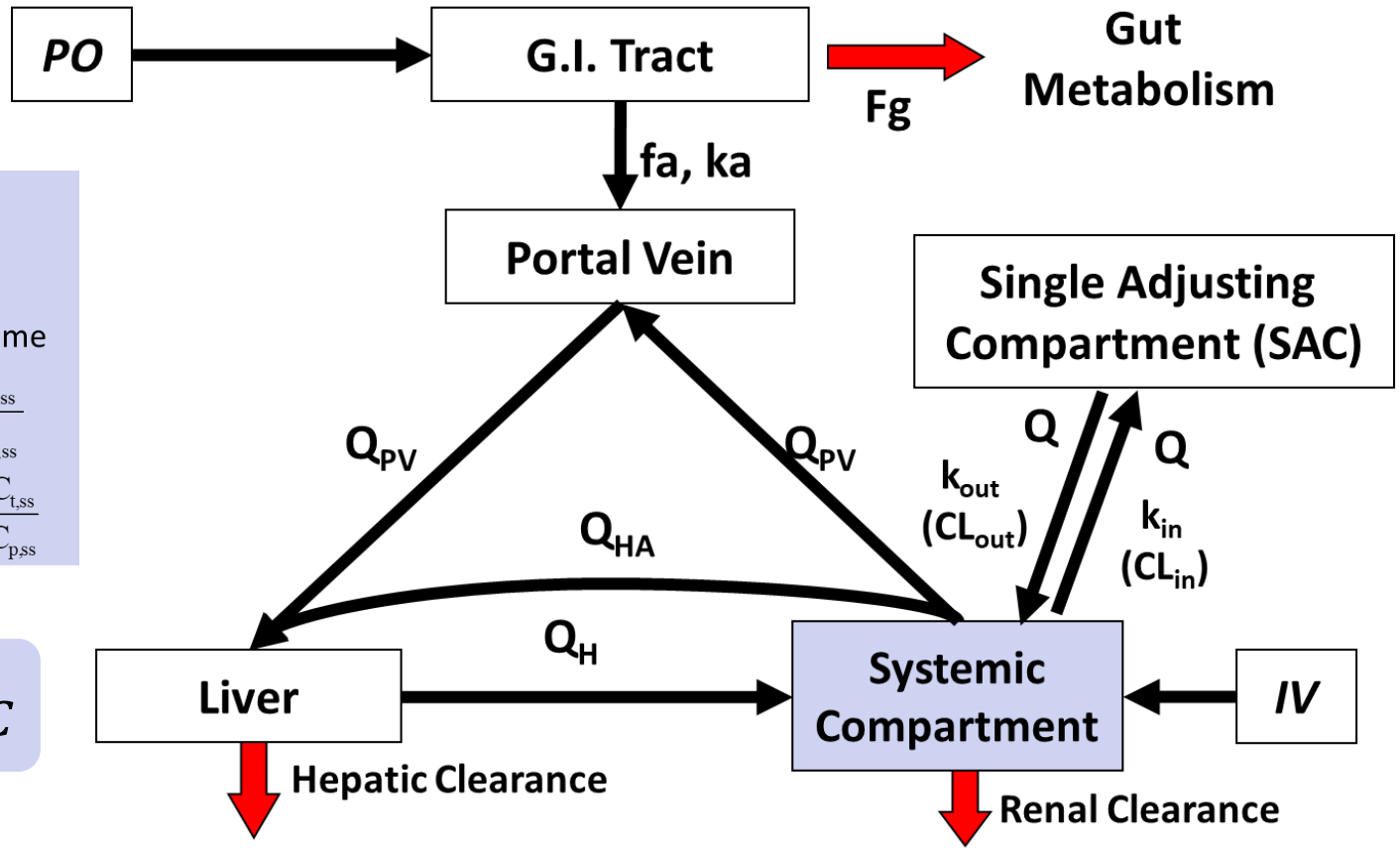
V_p = volume of plasma; V_e = volume of erythrocyte; V_t = tissue (t) volume

E:P = Erythrocyte : Plasma partition coefficient $E:P = \frac{C_{e,ss}}{C_{p,ss}}$

$P_{t:p}$ (or K_p) = Tissue Plasma partition coefficient $P_{t:p} = K_p = \frac{C_{t,ss}}{C_{p,ss}}$

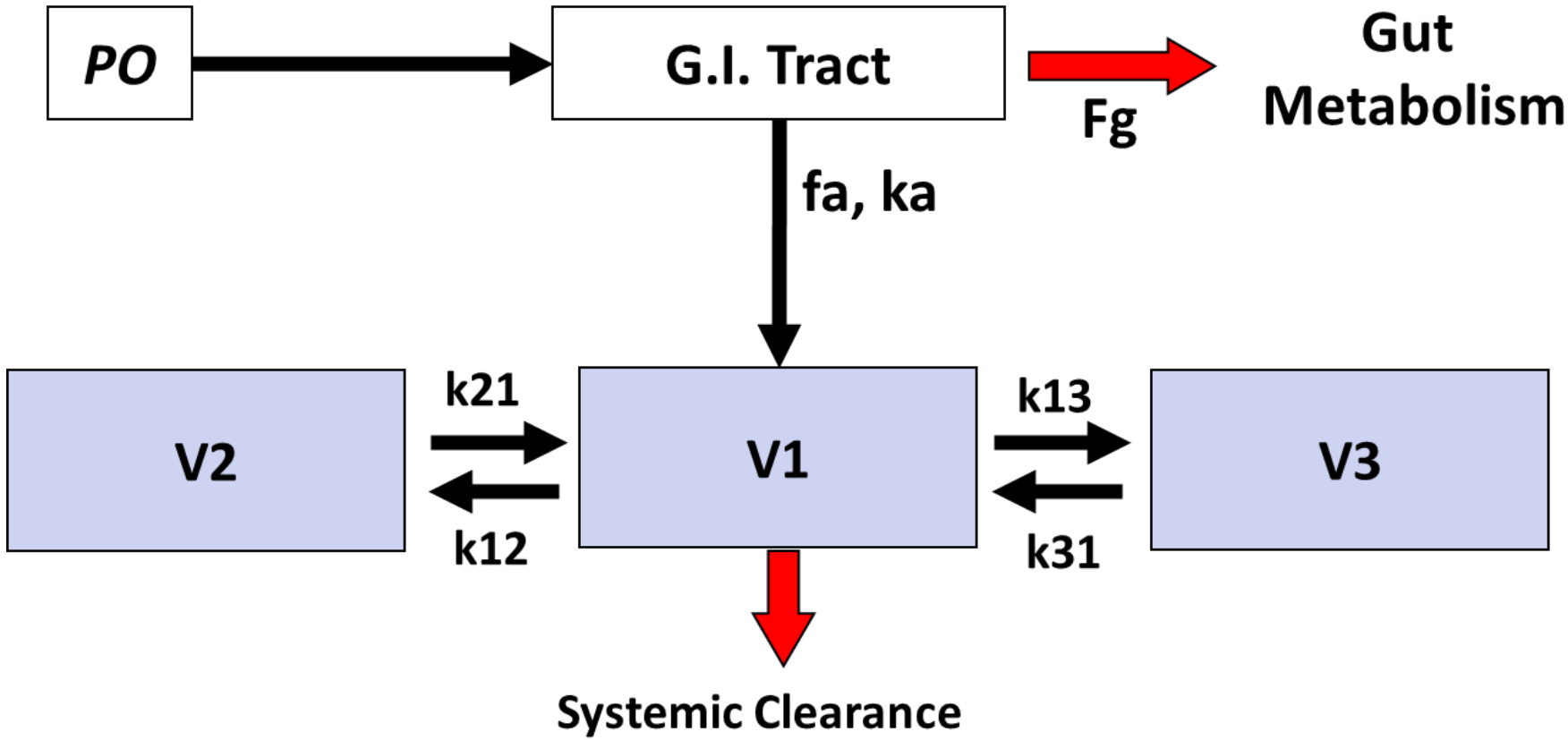
$$V_{sys} = V_{ss} - V_L \cdot K_{p:liver} - V_{SAC}$$

"middle out" approach



Drug Distribution Models – Compartmental Models

- ○ Minimal PBPK Model
- ○ Full PBPK
- ◉ Compartmental



Maybe used when IV PK known and when model is being used to predict/verify absorption only

Drug Distribution Models – Full PBPK

- ○ Minimal PBPK Model
- ◉ Full PBPK
- ○ Compartmental

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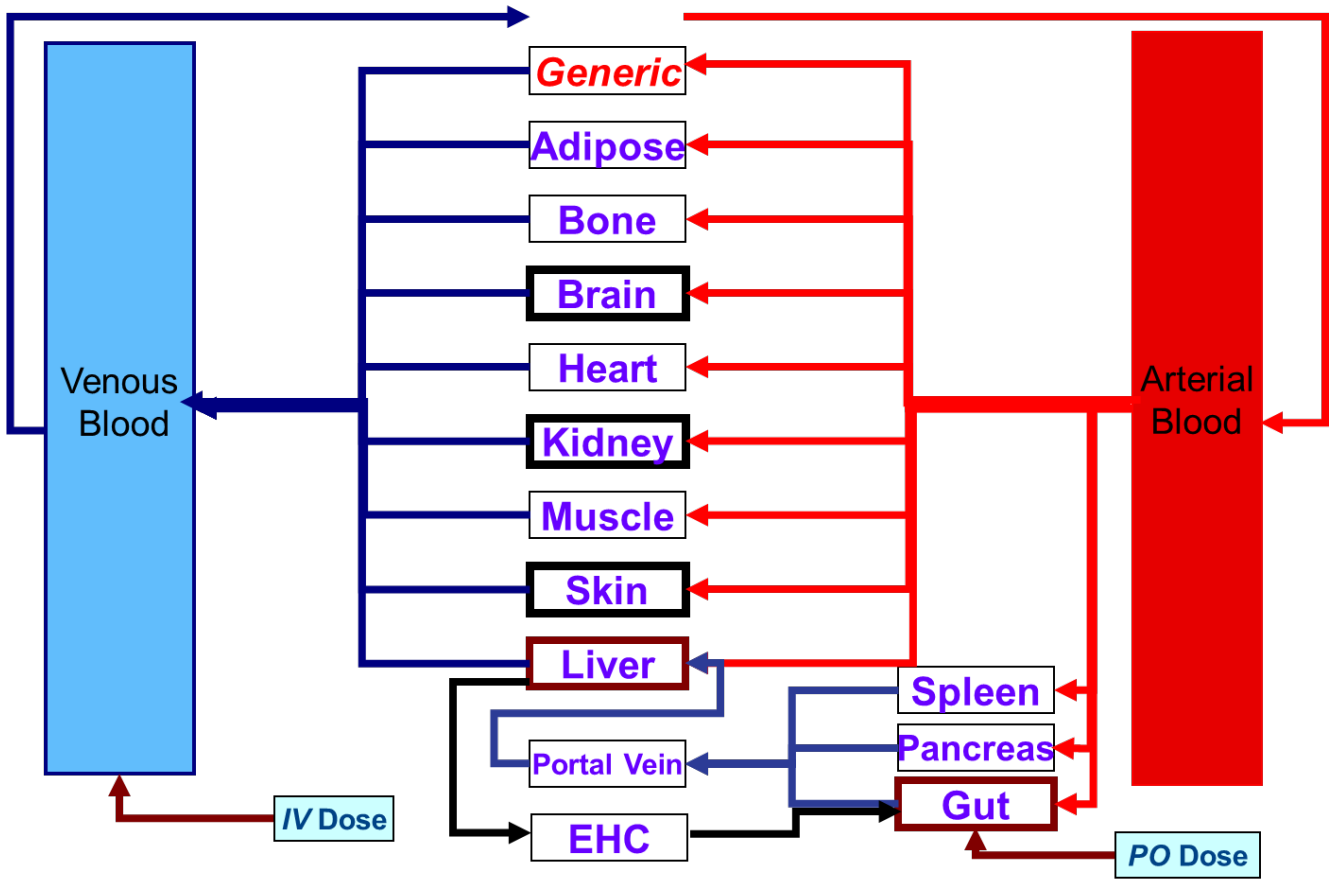
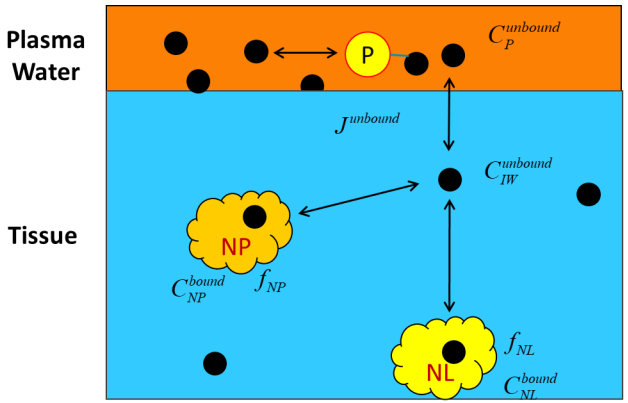
"bottom up" approach most frequently used in FIH predictions



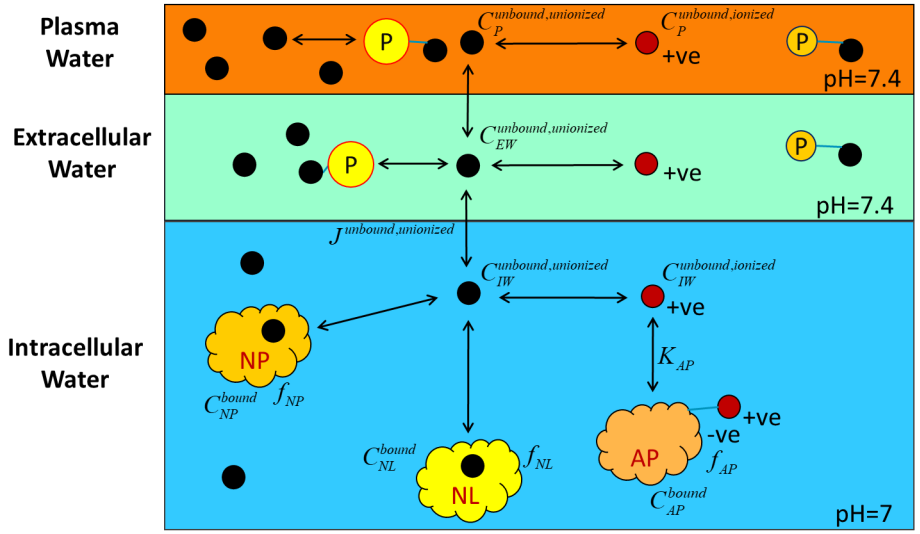
Prediction of Distribution using Kp prediction methods (1-3)

Method 1 Poulin and Theil (Berezhkovskiy, 2004)



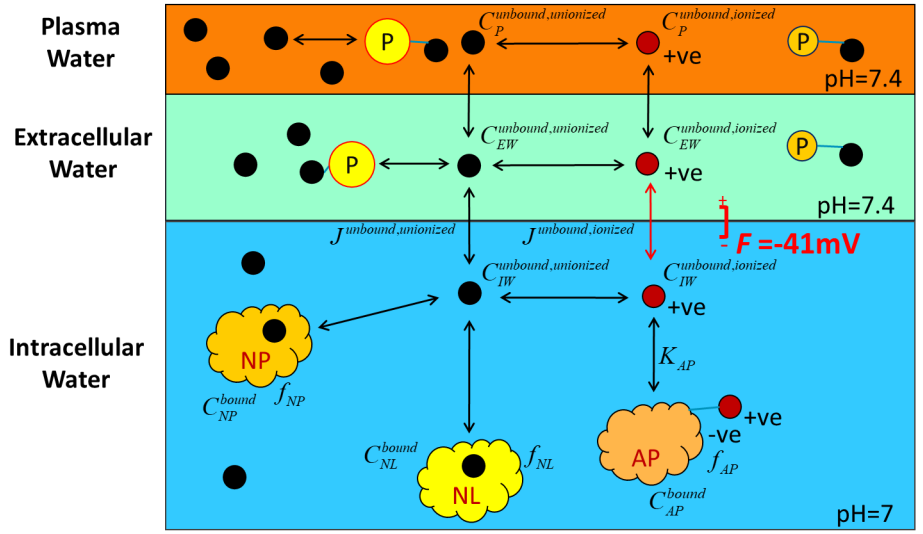
NL: Neutral Lipids
NP: Neutral Phospholipids P: Proteins

Method 2 Rodgers & Rowland (R&R)



NL: Neutral Lipids
NP: Neutral Phospholipids
AP: Acidic Phospholipids
P: Proteins

Method 3 R&R with ion permeability



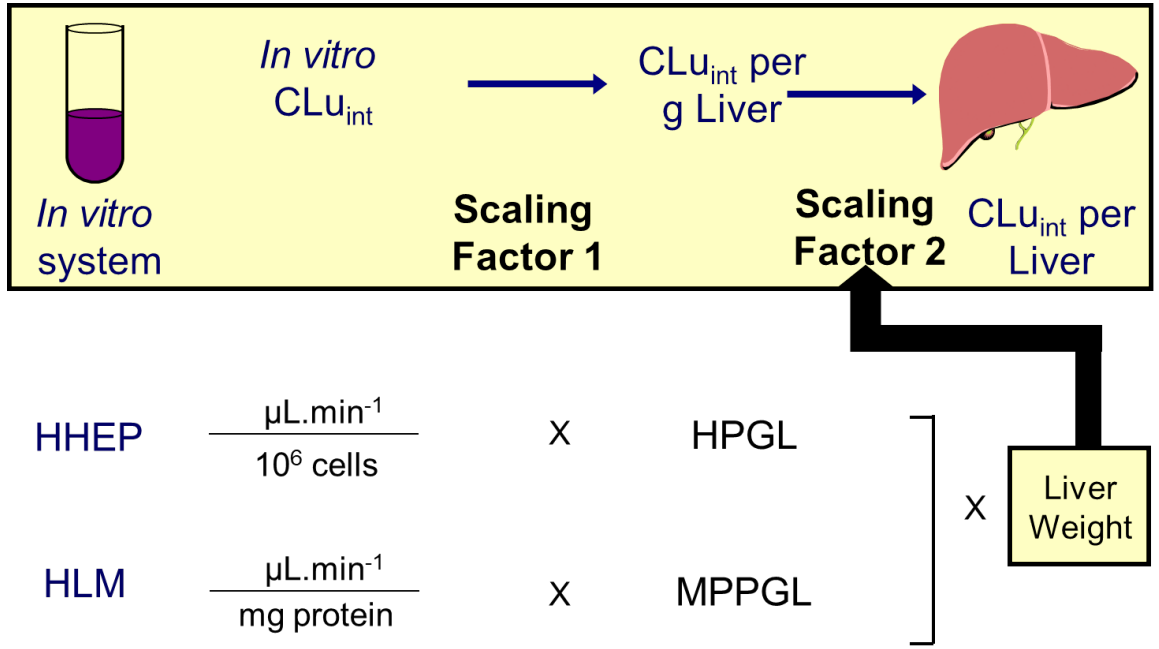
NL: Neutral Lipids
NP: Neutral Phospholipids
AP: Acidic Phospholipids
P: Proteins

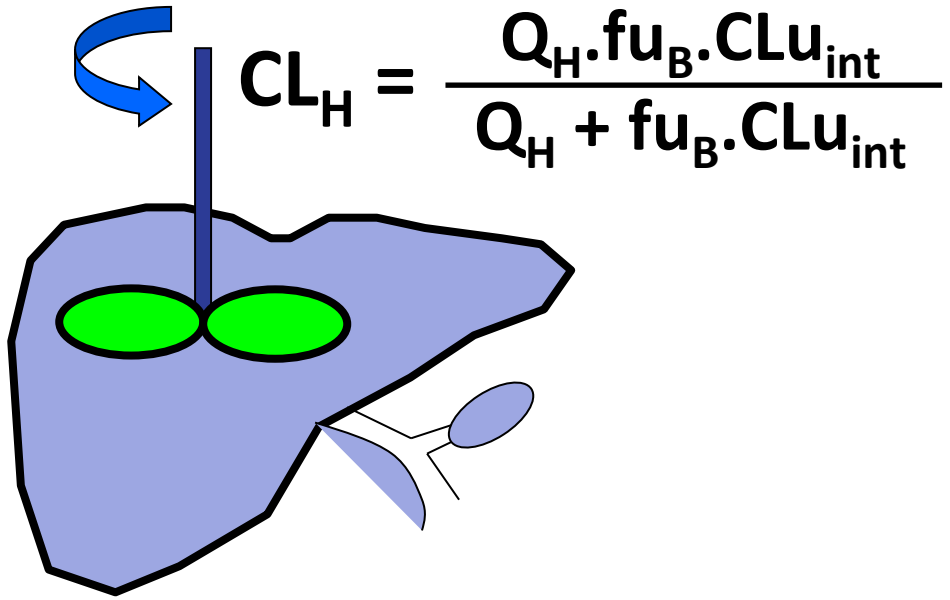
Increasing complexity

Note - may also compare these methodologies to allometry generally predicts Vss well to provide more confidence

Prediction of Clearance using in vitro and in vivo data

Prediction of CL from in vitro data

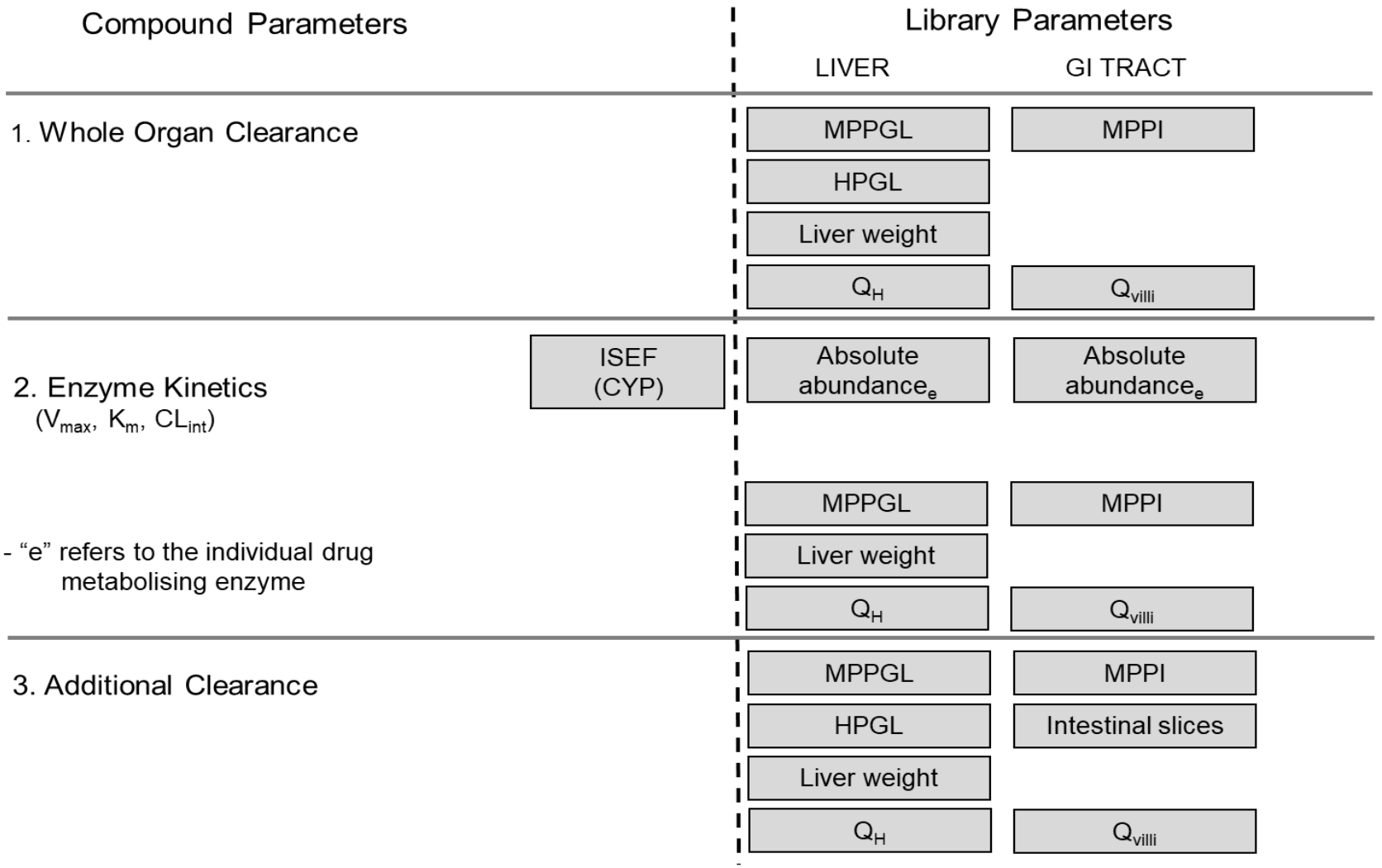




Prediction of excretion processes should also be considered (biliary and renal)

Allometric scaling from multiple or single species

Flexibility for Variable Input & Added Complexity



CL estimates from allometry/single species scaling can also be used

Prediction of Excretion in Simcyp Discovery

Quantitatively the two most important mechanisms of drug excretion are:

Renal Clearance

- Passive and active processes can be important
- Can be predicted allometrically and included in the PBPK model in Simcyp Discovery

Biliary Clearance

- If this is quantitatively important for drug elimination it is invariably an active (transporter driven) process
- It is possible to account for biliary excretion as an overall process and by a specific transporter in Simcyp Discovery

PBPK Strategies from the Literature – Pre-Clinical Studies

Early IVIVE-PBPK studies in rat (pre-2008)

- Volume predictions generally within 2-fold (range 1.2-1.9-fold, n= 118 compounds)
- General under-prediction of clearance (AFE 1.8 – 2.5-fold)
- Reasonable prediction of tissue levels
  - Parrott *et al*, J Pharm Sci, 94, 2327, 2005
  - De Buck *et al* DMD, 35, 649, 2007

Jones *et al*, Xenobiotica, 42, 94, 2012

- PBPK approaches used to simulate exposure for early toxicology studies
- More accurate than using linear scaling from low dose *in vivo* studies (n=39 compounds)

How Successful are Human IVIVE-PBPK Strategies?

- Generally a pre-validation step was undertaken in pre-clinical PBPK models
- Human PBPK evaluated using HLM or Hep CL_{int} for IV & oral dosing
  - AUC, T_{max}, C_{max}, F, CL, V_{ss} within two-fold for > 50% of compounds
    - Jones *et al.,* 2006, Clin PK, 45, 511, 2006 (n=19, *p.o*)
    - De Buck *et al*., 2007, DMD, 35, 1766 (n=26, *i.v* & *p.o*)
    - Jones *et al.,* 2011, Clin PK, 50, 331 (n=20,*i.v)*

PBPK *vs*. single species scaling (allometry) - Jones *et al.,* 2011

Table V. Global prediction accuracy of clearance (CL) using all approaches

Prediction measure	SSS from rat	SSS from dog	HLM[a]
% within 2-fold error [3-fold error] of observed value	63 [84]	78 [89]	67 [75]
Average fold error	1.8	1.7	2.0

a For CYP substrates only.

CYP = cytochrome P450; **HLM** = human liver microsomes; **SSS** = single-species allometric scaling.

CL predictions from HLM perform reasonably vs. Single Species Scaling (SSS)

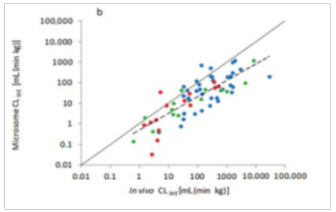
Accuracy of CL and CLint using IVIVE Methods

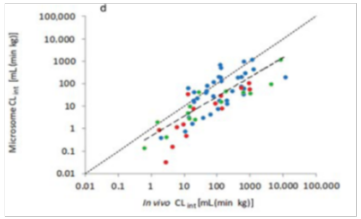
System	AFE	Reference
HLM	2.3	Obach DMD 27, 1350, 1999
	6.2	Ito, Pharm Res, 22, 103, 2005
	2.3	Stringer, Xeno, 38, 1313, 2008
	2.2	Ring, J Pharm Sci, 100, 490 ,2011
	5	Hallifax, Pharm Res, 27, 2150, 2010
	2.0	Jones, Clin Pk, 50, 311, 2011
Hepatocytes	2.4	De Buck DMD, 35, 1766, 2007
	5.2	Stringer, Xeno, 38, 1313, 2008
	5.0	Hallifax 2011
	7.6	Naritomi DMD 31, 580, 2003
Recombinant CYP	1.53 PT, 2.15 WS	Stringer DMD, 37,1025, 2009

Generally many literature studies shows under-prediction from in vitro systems
Correct using an empirical scaling factor – Specific to your system!

Correction Factors to Improve IVIVE for Clearance

Hallifax and Houston, J Pharm Sci, 2012, 101, 2645

Eq 1 

Eq 2 

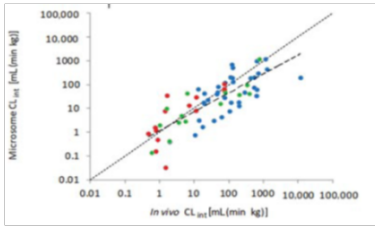
Eq 3 

Table 4. Comparison of methods (Conventional, Berezhkovskiy, Poulin and Bias-Corrected Conventional) for *in vivo* CL_{int}, in terms of precision of prediction (root mean squared error) and fitted log-linear relationship parameter values, for hepatocytes and microsomes

In vitro System	*In vivo* Calculation Method	*n*	RMSE	Slope	Intercept	*r*
Hepatocytes	Conventional	89	0.82	0.51	0.30	0.73
	Berezhkovskiy	89	0.79	0.47	0.42	0.66
	Poulin	89	0.63	0.48	0.57	0.71
	Conventional (bias corrected)	89	0.59	0.51	0.88	0.73
Microsomes	Conventional	64	0.93	0.80	−0.29	0.81
	Berezhkovskiy	64	0.84	0.97	−0.31	0.79
	Poulin	64	0.69	0.79	0.079	0.80
	Conventional (bias corrected)	64	0.63	0.80	0.40	0.81

Conventional bias correction method was superior

http://dmd.aspetjournals.org/content/suppl/2017/10/20/dmd.117.077040.DC2

1521-009X/45/11/1178–1188$25.00
Drug Metabolism and Disposition
https://doi.org/10.1124/dmd.117.077040
Drug Metab Dispos 45:1178–1188, November 2017

Commentary

Clearance Prediction Methodology Needs Fundamental Improvement: Trends Common to Rat and Human Hepatocytes/Microsomes and Implications for Experimental Methodology

F. L. Wood,[1] J. B. Houston, and D. Hallifax

Centre for Applied Pharmacokinetic Research, Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom

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TABLE 3

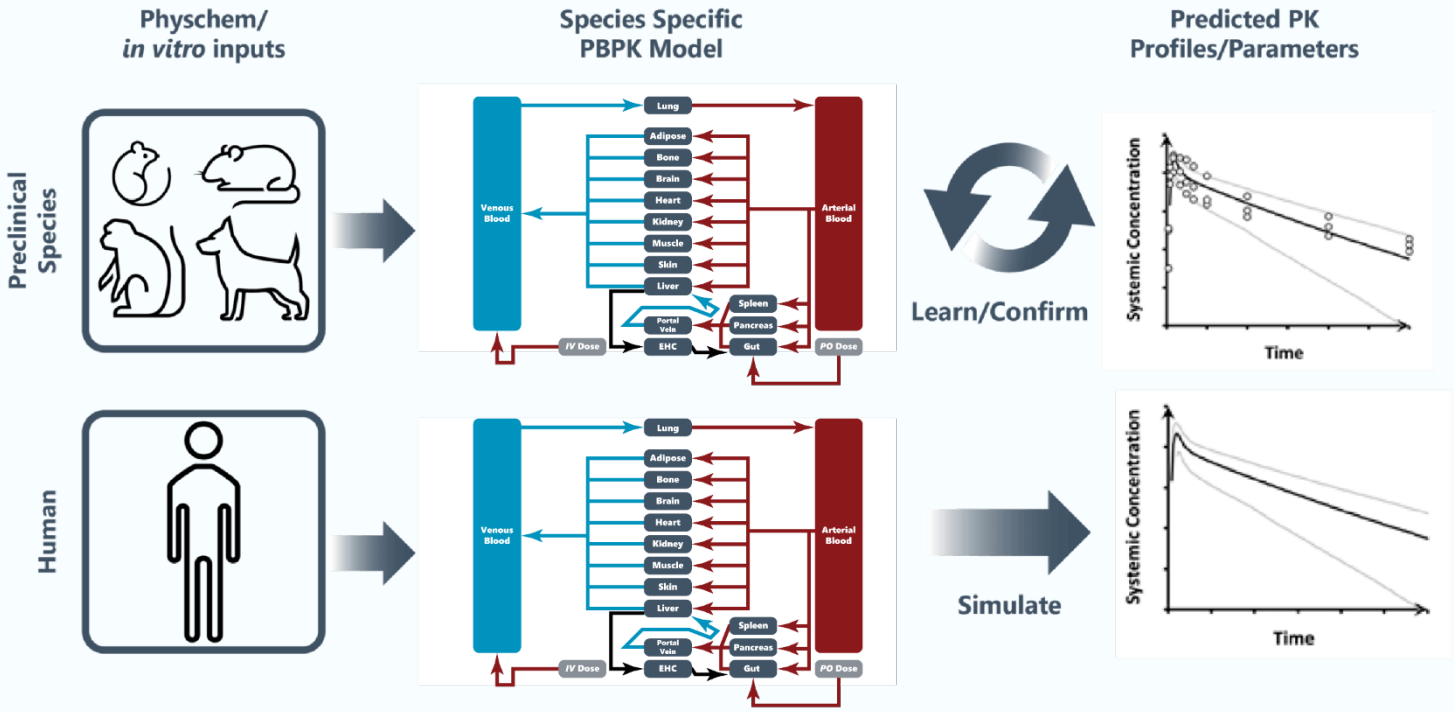
Average individual ESF for predicted $CL_{int,u}$ according to level of observed $CL_{int,u}$ for human and rat hepatocytes and liver microsomes

Observed $CL_{int,u}$	ESF							
	Human				Rat			
	Hepatocytes		Microsomes		Hepatocytes		Microsomes	
	Log Average	*n*	Log Average	*n*	Log Average	*n*	Log Average	*n*
ml/min/kg								
<10	0.61	21	0.70	17	0.13	3	0.086	3
10–100	3.9	32	1.8	20	1.6	12	0.83	8
100–1000	7.1	40	4.6	34	3.2	67	1.7	34
1000–10,000	22	6	7.5	10	7.2	37	2.5	20
>10,000	1200	2	58	2	180	9	230	6

ESFs to account for underprediction in rat & human
Works well across projects

Applications of PBPK modelling in Discovery

FIH Dose Prediction

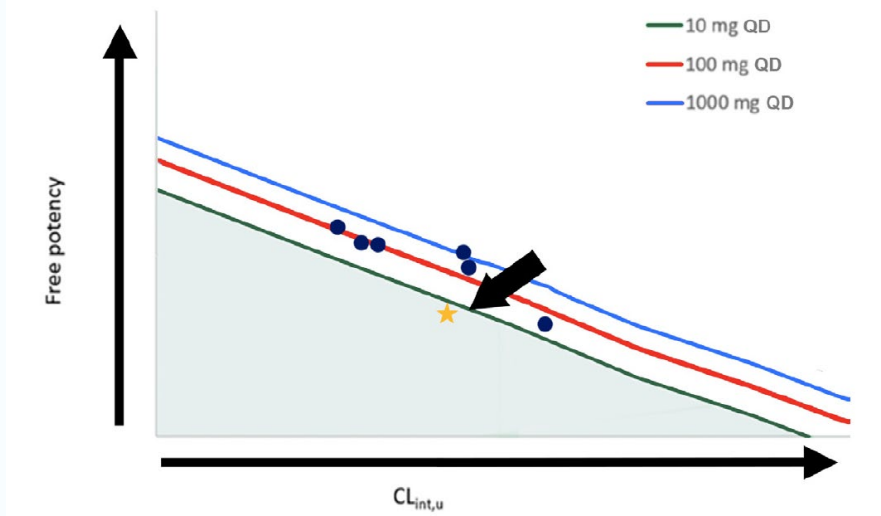


Predict plasma and tissue concentration profiles across species and in humans -> link to PD models

Mechanistic approach with good IVIVC with minimal in vivo data

Compound Triage and Pipeline Optimization

Defining laboratory objectives:



Compound ranking and selection:

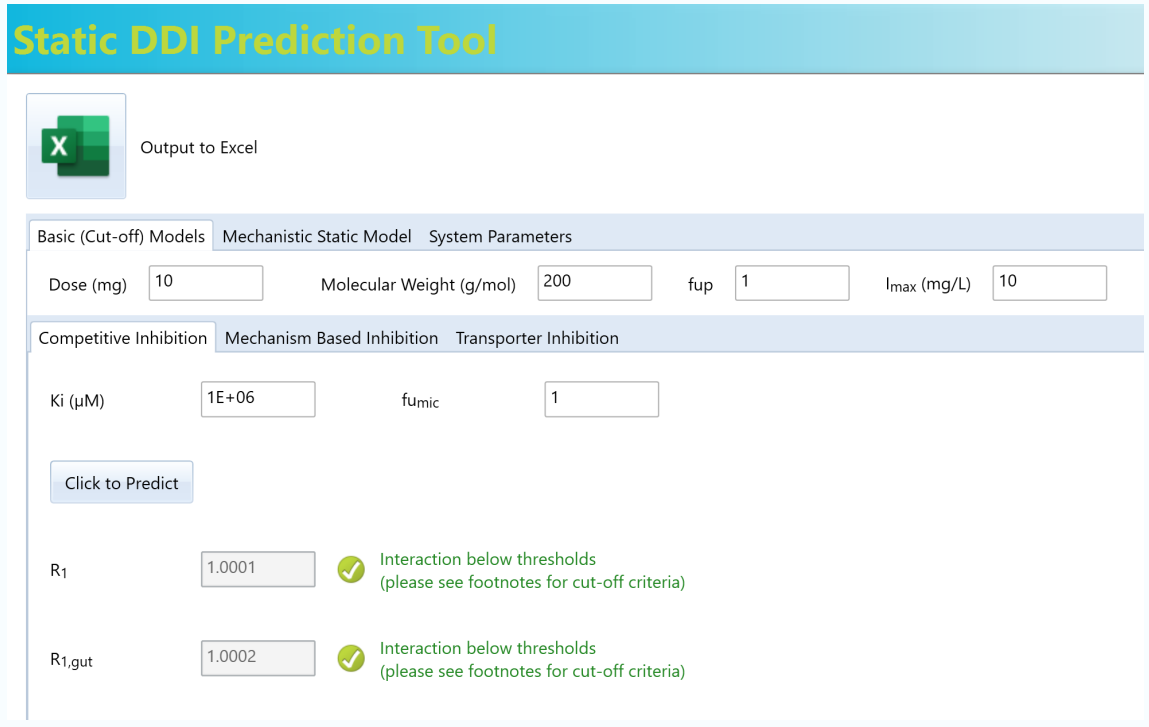
	CPD 1	CPD 2	CPD 3
CL	5	10	8
Potency	1	2	4
Dose	5	20	32

Applications of PBPK modelling in Discovery contd.

Early DDI Screening

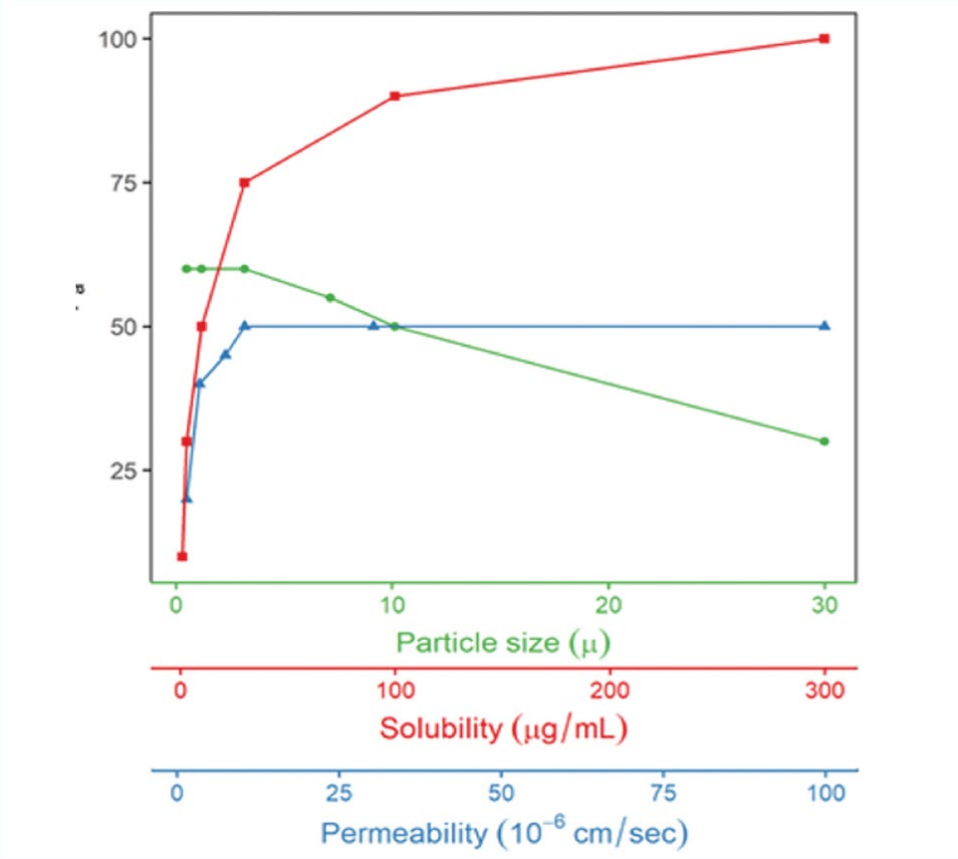
Uses regulatory guidance (EMA, FDA, PMDA) equations to calculate DDI risk

At both perpetrator and victim level



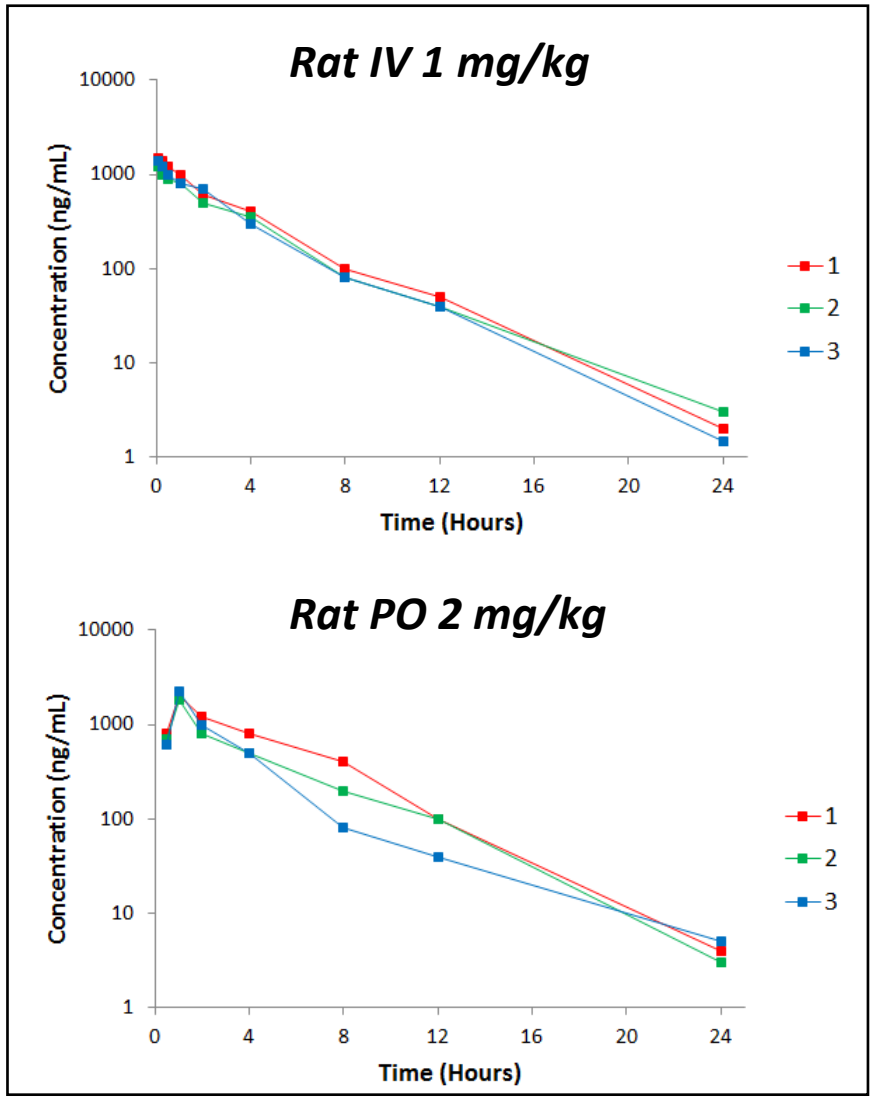
Early Formulation Simulation

Sensitivity analysis to guide formulation design -> maximize exposure for tox /optimize formulation



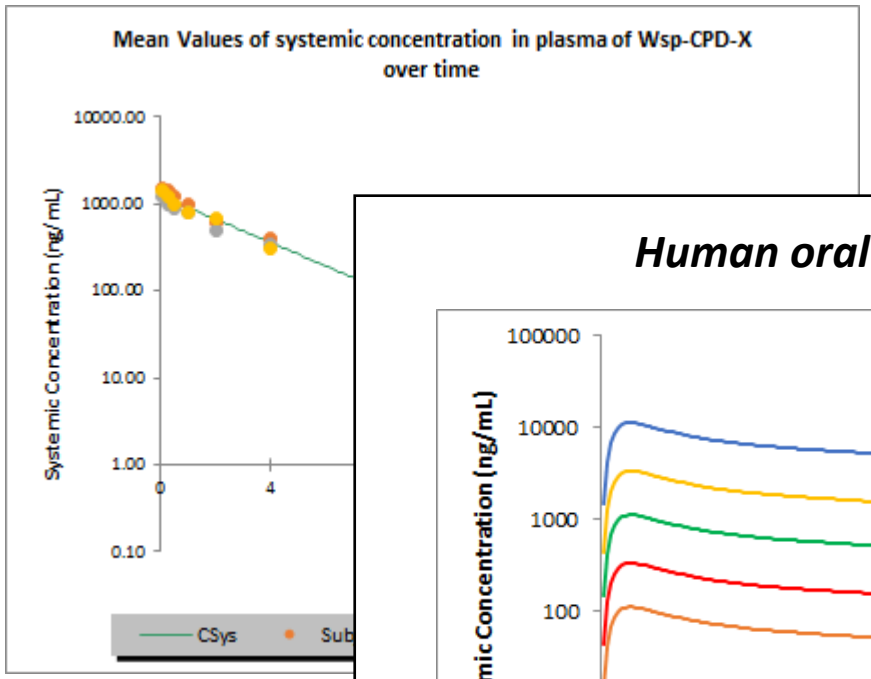
Case Study: ADME properties and model input parameters

Parameter	Value
MW g/mol	500
LogP	3.4
Charge	neutral
fu in plasma	0.01 (R), 0.009 (D), 0.012 (H)
B/P ratio	assumed to be 1
Microsomal CLint µl/min/mg	100 (R), 70 (D), 50 (H)
fu,mic	0.5
Solubility mg/mL	0.2
Permeability	high - predicted from physchem

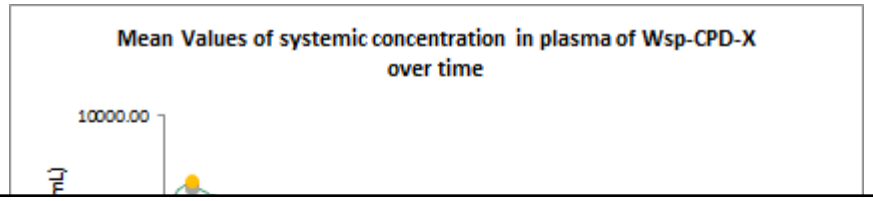


Case Study – Preclinical model validation & FIH simulation

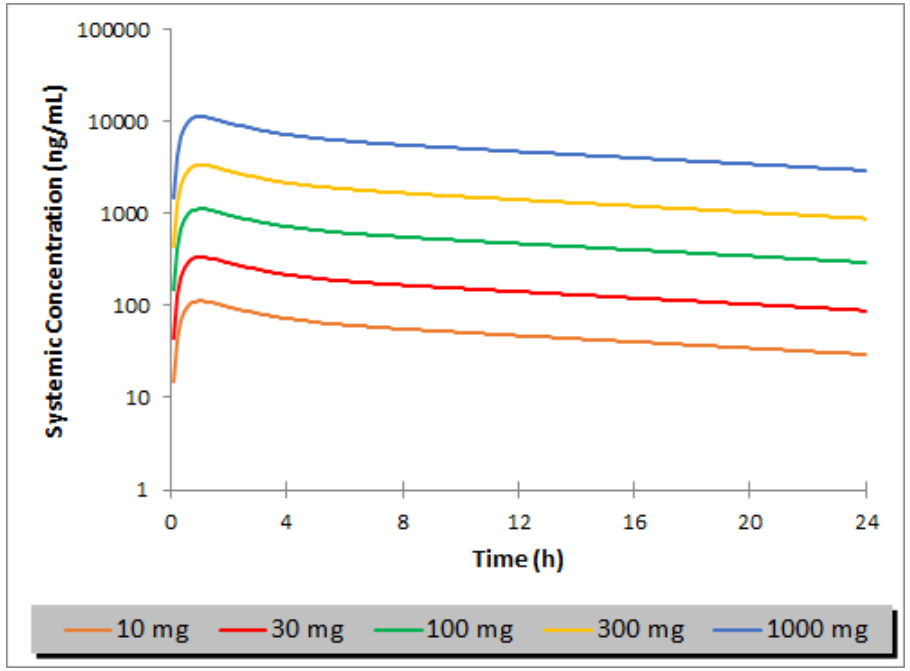
Rat IV 1 mg/kg



Rat PO 2 mg/kg



Human oral simulation across a range of doses



Dose (mg)	AUC (ng/mL.h)	CMax (ng/mL)	TMax (h)	t 1/2 (terminal) (h)
10	1257	113	1.00	17.64
30	3770	338	1.00	17.64
100	12567	1127	1.00	17.64
300	37702	3382	1.00	17.64
1000	125672	11274	1.00	17.64

	Basic static	Mechanistic static
CYP3A4	YES	YES
CYP1A2	YES	NO
P-gp	YES	YES

General Guidance for PBPK modelling in Discovery Space

- Always perform pre-verification steps in preclinical species to build confidence in data and assumptions

- CL is generally underpredicted from in vitro systems – Wood scalar often incorporated to account for this with some success
- Explore a range of CL methodologies if uncertainty in CL mechanism

- Vss/distribution is generally well predicted across species –> approach to compare tissue composition equations against Vss,u the same across species

- Permeability normally well predicted with using in vitro data or MechPeff model
- Explore aqueous solubility and biorelevant solubility to predict dissolution -> if data is limited consider using solution dosing

Why use Simcyp Discovery?

- Allows integration of all available discovery data to provide an informed PK and dose projection with minimal data
- Allows scaling from in vitro data with minimal in vivo data
- Informs decision making at all stages of drug discovery
- Quick and easy to use

Thank you

Accelerating Medicines, Together