PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELLING FOR FIRST-IN-HUMAN PREDICTIONS

Neil Miller, Micaela Reddy, Aki Heikkinen, Viera Lukacova & Neil Parrott

All in-vivo studies were conducted in accordance with local regulations for animal treatment

Hypothesis

- PBPK modelling, with verification of predictive performance first performed in preclinical species, is superior to empirical methods for predicting pharmacokinetics

Requirements for hypothesis testing

1. A defined PBPK strategy for PK predictions, based on best practices and experience across companies
2. Applying the proposed PBPK strategy with integrated ADME PBPK decision trees across pharmaceutical companies will enable a true evaluation of PBPK modelling in drug discovery

Jones HM, Parrott N, Jorga K, Lavé T. A novel strategy for physiologically based predictions of human pharmacokinetics. Clin Pharmacokinet. 2006;45(5):511–42

PBPK strategy for FIH predictions

- Updated the strategy of Jones et al to include new knowledge and additional flow diagrams for each essential component of a FIH prediction
- The strategy has been updated based on a comprehensive review of subsequent publications and on the combined knowledge and experience of the authors who are all PBPK specialists and members of the GastroPlus User Group Steering Committee
- Generally applicable to PBPK modelling, with only some components specific to GastroPlus

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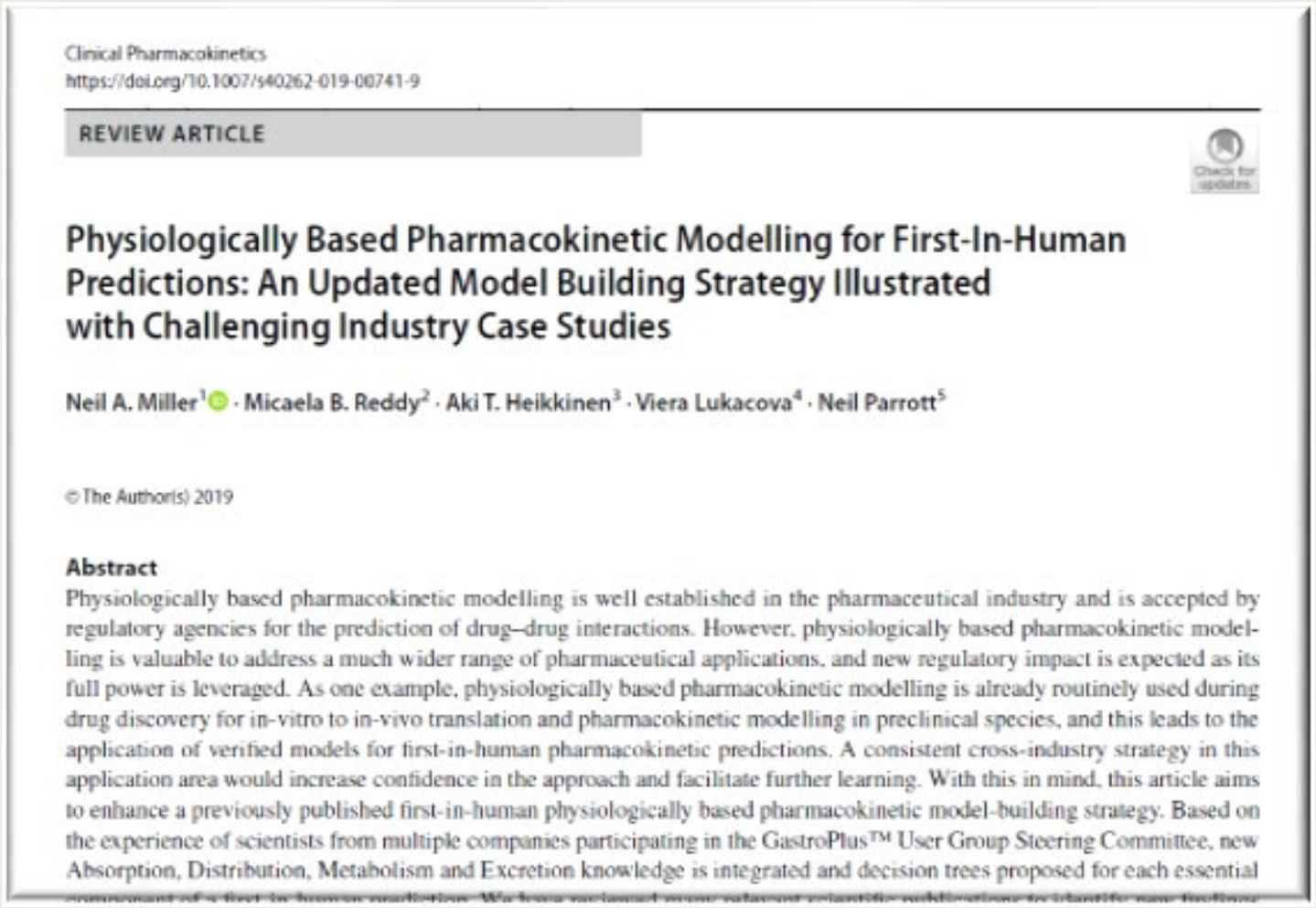
PBPK strategy for FIH predictions



Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-019-00741-9

REVIEW ARTICLE

Physiologically Based Pharmacokinetic Modelling for First-In-Human Predictions: An Updated Model Building Strategy Illustrated with Challenging Industry Case Studies

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Abstract

Physiologically based pharmacokinetic modelling is well established in the pharmaceutical industry and is accepted by regulatory agencies for the prediction of drug–drug interactions. However, physiologically based pharmacokinetic modelling is valuable to address a much wider range of pharmaceutical applications, and new regulatory impact is expected as its full power is leveraged. As one example, physiologically based pharmacokinetic modelling is already routinely used during drug discovery for in-vitro to in-vivo translation and pharmacokinetic modelling in preclinical species, and this leads to the application of verified models for first-in-human pharmacokinetic predictions. A consistent cross-industry strategy in this application area would increase confidence in the approach and facilitate further learning. With this in mind, this article aims to enhance a previously published first-in-human physiologically based pharmacokinetic model-building strategy. Based on the experience of scientists from multiple companies participating in the GastroPlus™ User Group Steering Committee, new Absorption, Distribution, Metabolism and Excretion knowledge is integrated and decision trees proposed for each essential

https://link.springer.com/article/10.1007/s40262-019-00741-9

Key points

- **Join in the assessment:** try out the proposed strategy for FIH predictions, based on best practices and experience across companies, for yourself
- **Help determine:** if PBPK model verification in preclinical species, which has not always been included in assessments of first-in-human pharmacokinetic predictions, is critical to build confidence and improve accuracy
- **Remember:** uncertainty analysis is a key consideration to obtain maximal value from first-in-human PBPK predictions

Decision trees for each essential component of a first-in-human (FIH) prediction

1. **QSPR plus PBPK assessment** to identify the major challenges of modelling for a specific molecule
2. **Metabolism and Elimination** for quantitative understanding of the main mechanism(s) of drug clearance
3. **Distribution** to understand the drivers of tissue distribution
4. **Oral Absorption** to decipher the multifactorial process
5. **Gut wall metabolism** for assessing the impact on oral exposure
6. **Uncertainty and Variability Analyses** as exploration of uncertainty is critical because of unknown factors at this stage

QSPR plus PBPK assessment

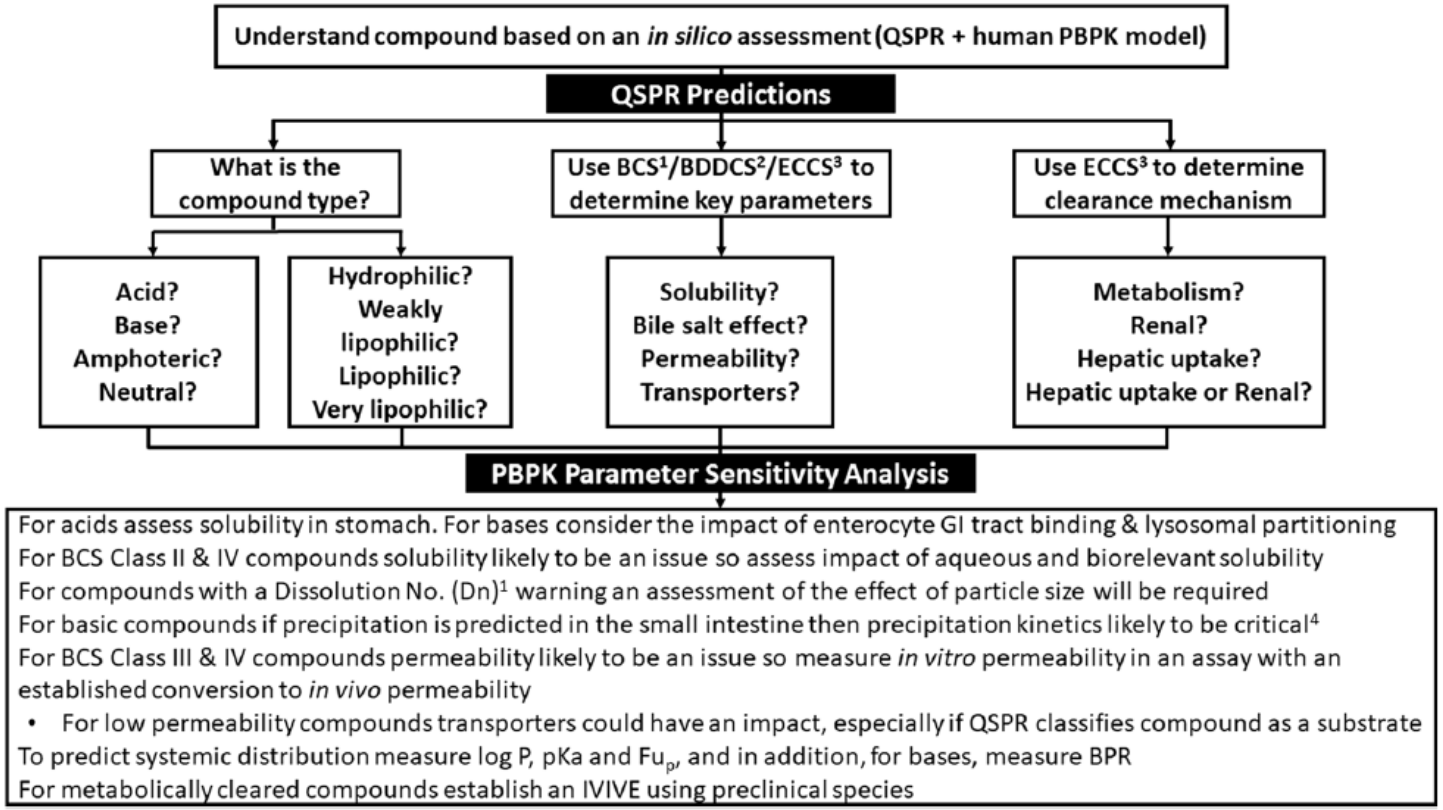


Fig. 1 Compound assessment from structure using quantitative structure–property relationship (QSPR) plus physiologically based pharmacokinetic (PBPK) modelling [27, 30–32]. *BCS* Biopharmaceutics Classification System, *BDDCS* Biopharmaceutics Drug Disposition Classification System, *BPR* blood/plasma ratio, *Dn* dissolution number (the ratio of small intestine transit time/idealised dissolution time), *ECCS* Extended Clearance Classification System, Fu_p Fraction unbound in plasma, *GI* gastrointestinal, *IVIVE* in-vitro in-vivo extrapolation. [1][27], [2][31], [3][30], [4][32]

Metabolism and Elimination

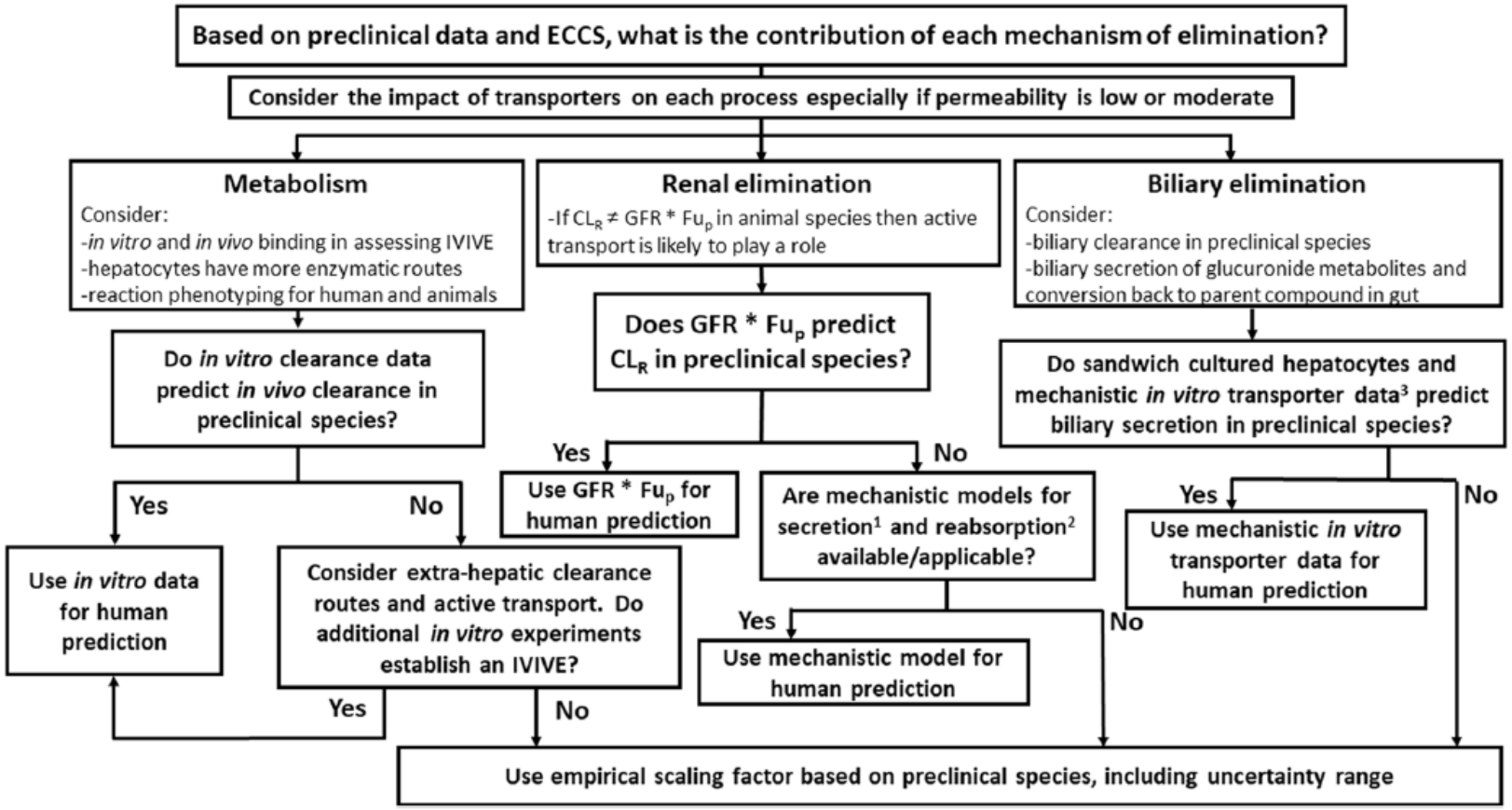


Fig. 2 Physiologically based pharmacokinetic modelling strategy for elimination [42–44]. CL_R renal clearance, $CL_{R,u}$ unbound renal clearance, *ECCS* Extended Clearance Classification System, Fu_p fraction unbound in plasma, *GFR* glomerular filtration rate, *IVIVE* in-vitro in-vivo extrapolation. [1][42], [2][43], [3][44]

Distribution

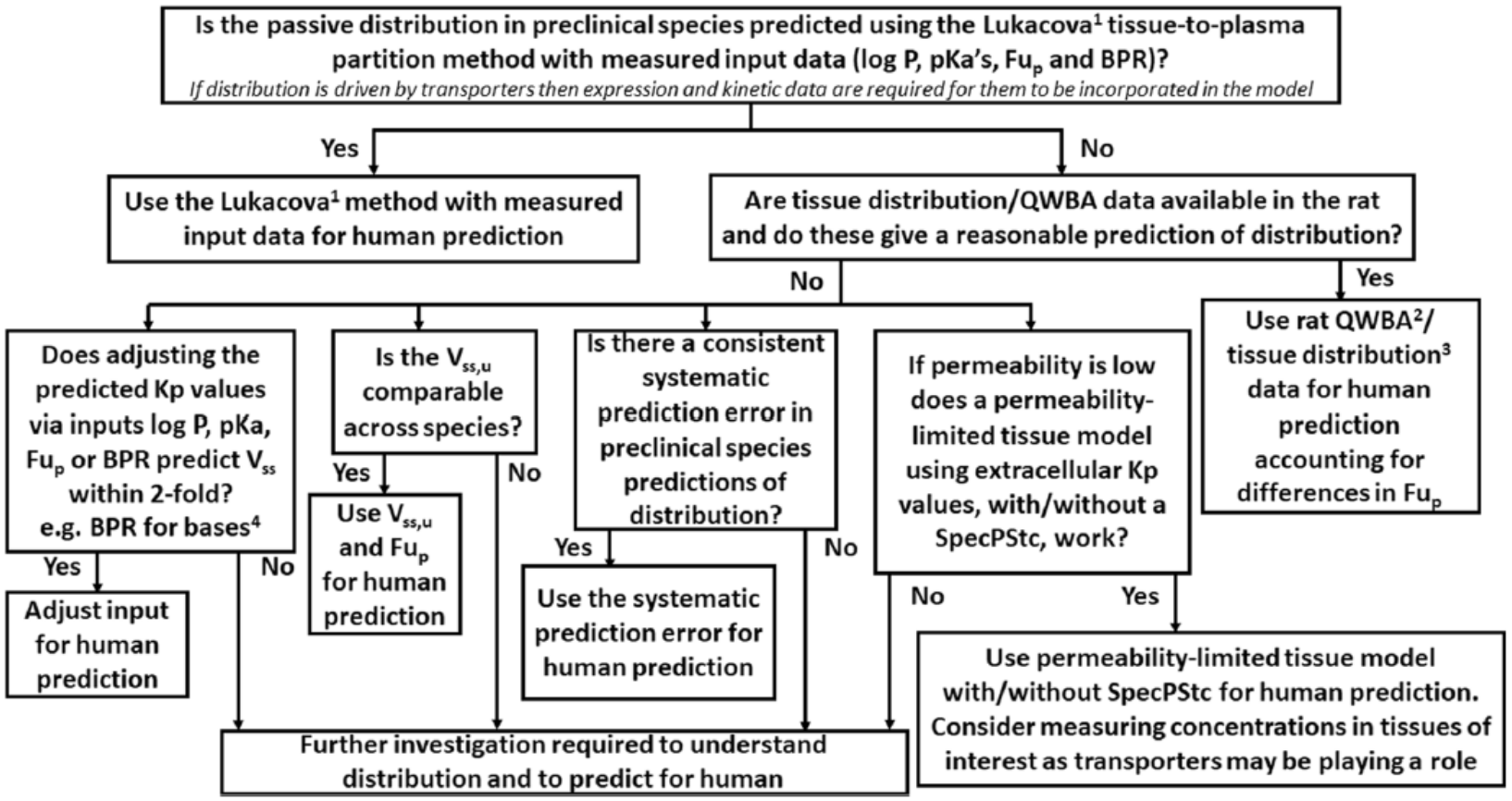


Fig. 3 Physiologically based pharmacokinetic modelling strategy for distribution [17, 50, 53, 55]. *BPR* blood/plasma ratio, Fu_p fraction unbound in plasma, K_p tissue-to-plasma partition coefficient, *SpecPStc* specific in-vivo diffusional clearance per millilitre of tissue cell volume. [1][50], [2][55], [3][17], [4][53]

Oral Absorption

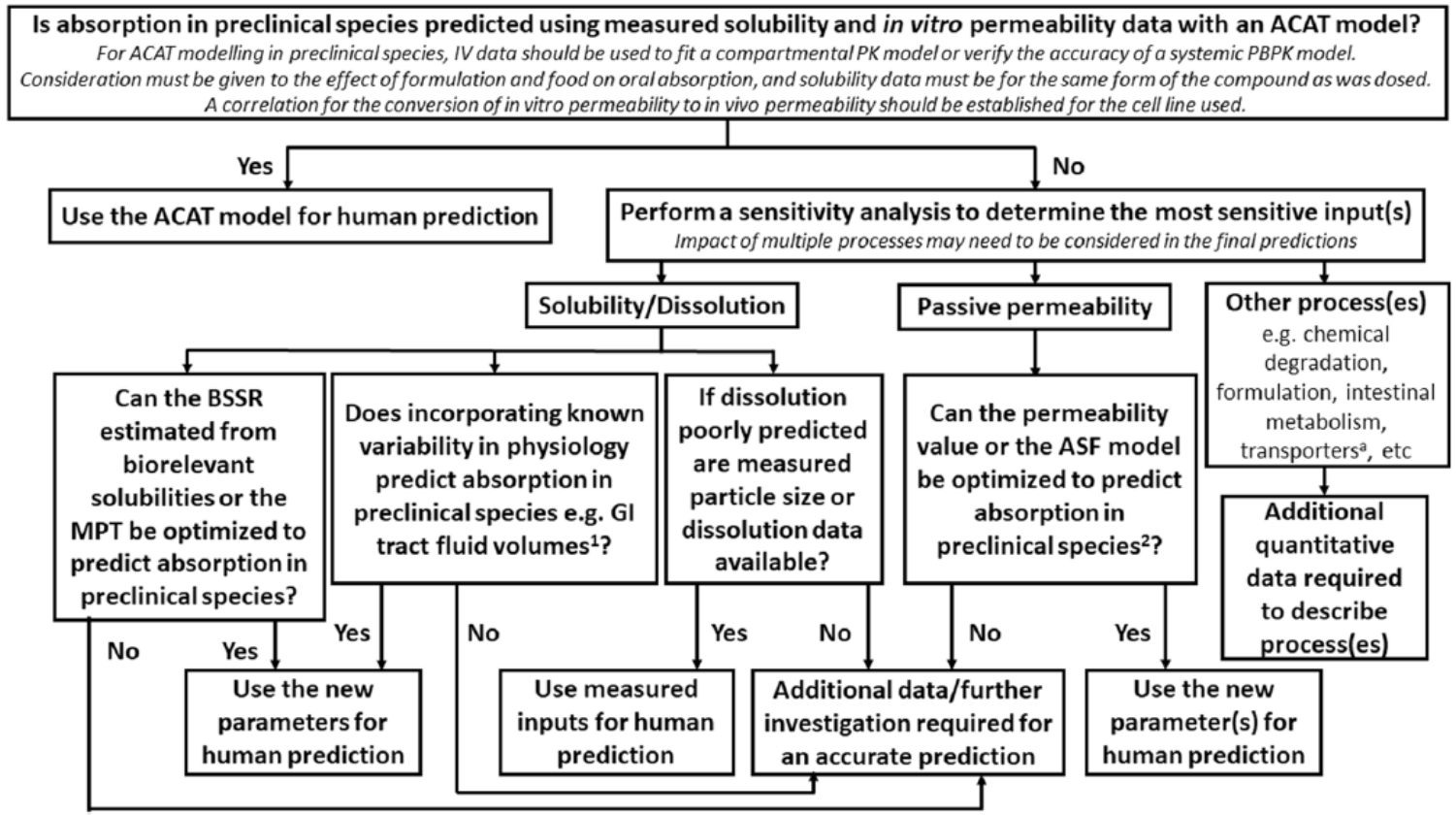


Fig. 4 Physiologically based pharmacokinetic modelling strategy for oral absorption [57, 58]. *ASF* absorption scale factors, *BSSR* bile salt solubilisation ratio, *MPT* mean precipitation time. [a] Other processes" transporters: efflux transporters can be incorporated in GastroPlus models with a simple method (e.g. adjusting permeability based on preclinical observations or in-vitro data) to more complex methods (e.g. specifically incorporating effects of transporters) [60–62]. [1][57], [2][58]

Gut wall metabolism

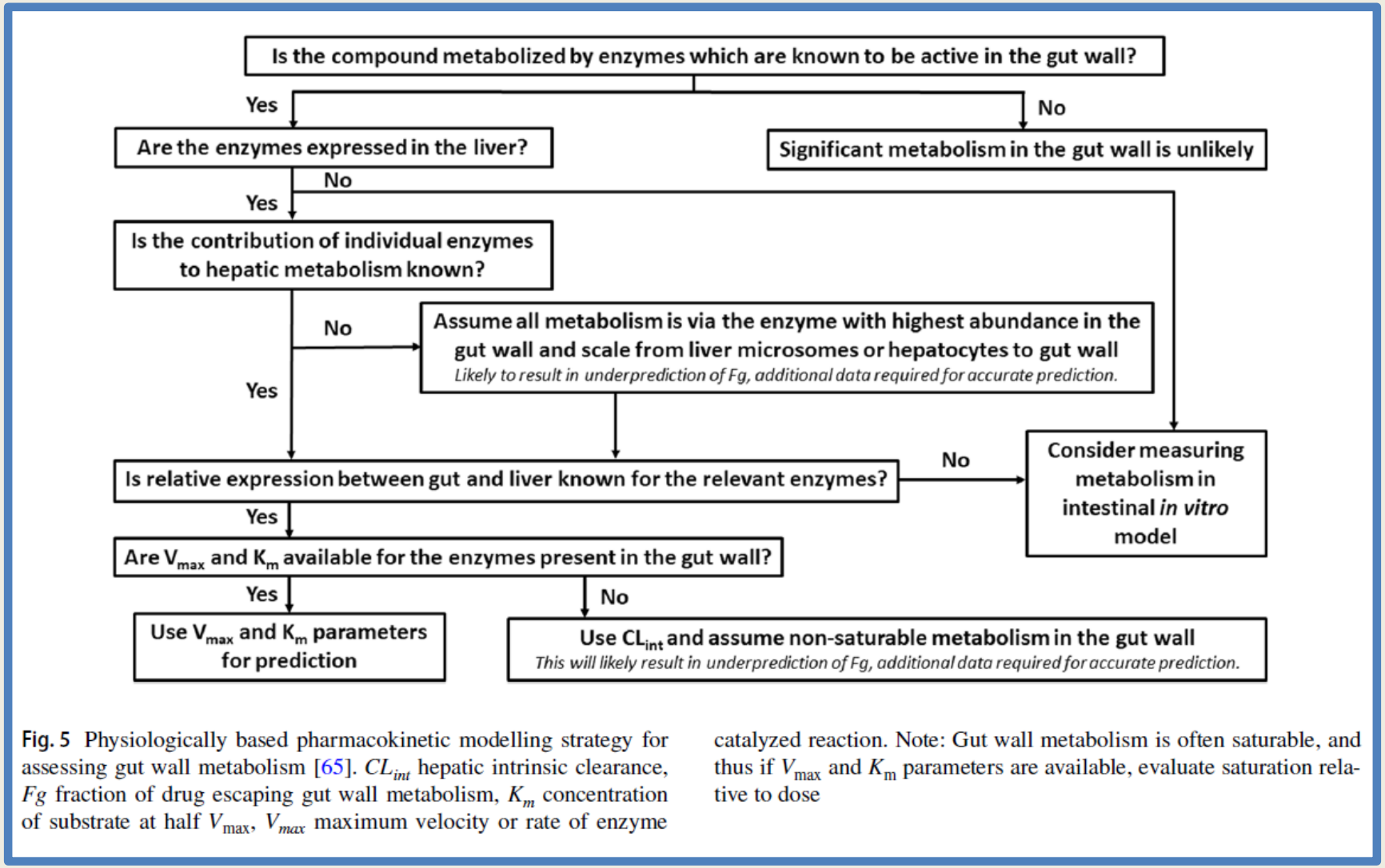


Fig. 5 Physiologically based pharmacokinetic modelling strategy for assessing gut wall metabolism [65]. CL_{int} hepatic intrinsic clearance, Fg fraction of drug escaping gut wall metabolism, K_m concentration of substrate at half V_{max}, V_{max} maximum velocity or rate of enzyme catalyzed reaction. Note: Gut wall metabolism is often saturable, and thus if V_{max} and K_m parameters are available, evaluate saturation relative to dose

Uncertainty and Variability Analyses

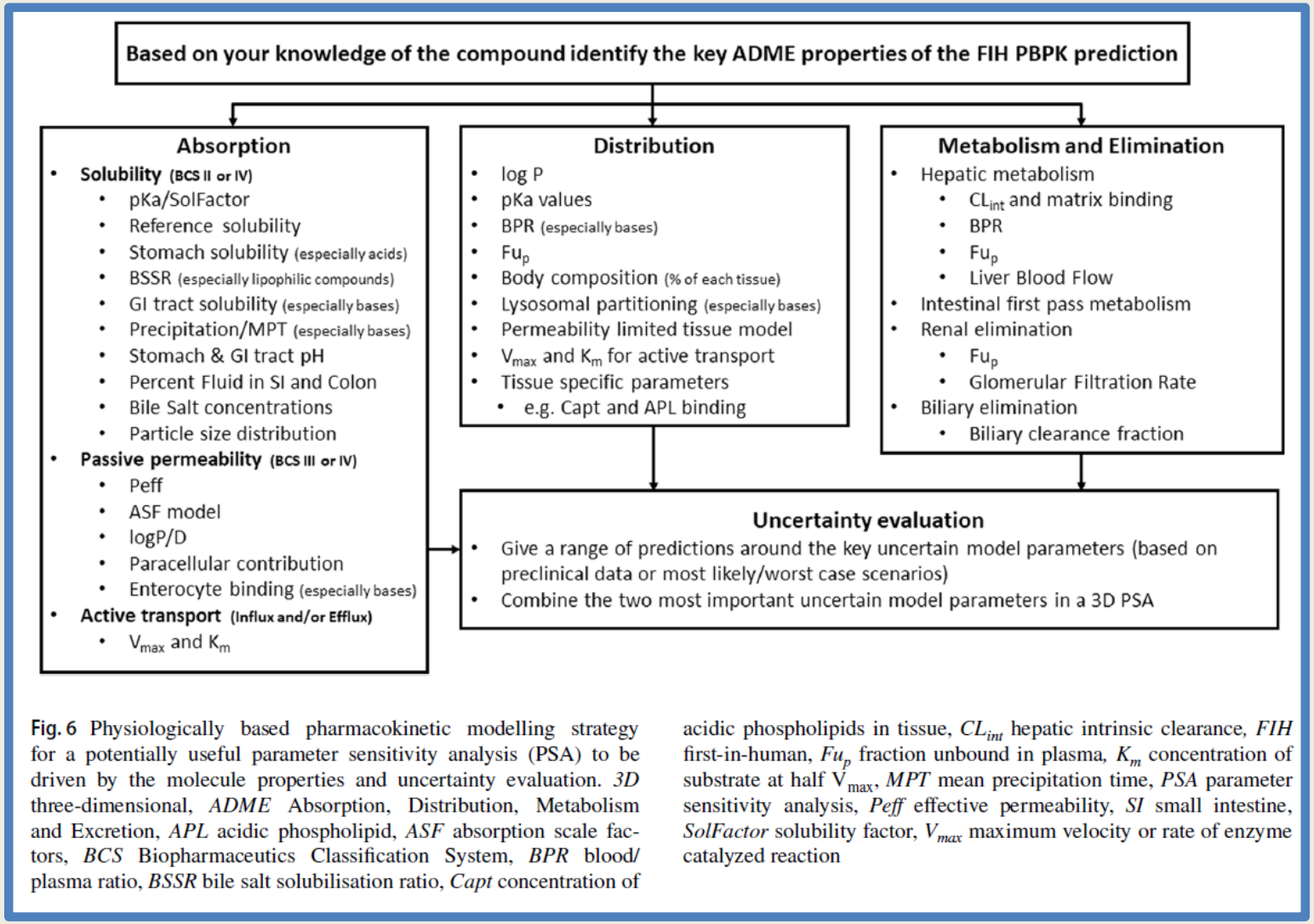


Fig. 6 Physiologically based pharmacokinetic modelling strategy for a potentially useful parameter sensitivity analysis (PSA) to be driven by the molecule properties and uncertainty evaluation. *3D* three-dimensional, *ADME* Absorption, Distribution, Metabolism and Excretion, *APL* acidic phospholipid, *ASF* absorption scale factors, *BCS* Biopharmaceutics Classification System, *BPR* blood/plasma ratio, *BSSR* bile salt solubilisation ratio, *Capt* concentration of acidic phospholipids in tissue, CL_{int} hepatic intrinsic clearance, *FIH* first-in-human, Fu_p fraction unbound in plasma, K_m concentration of substrate at half V_{max}, *MPT* mean precipitation time, *PSA* parameter sensitivity analysis, *Peff* effective permeability, *SI* small intestine, *SolFactor* solubility factor, V_{max} maximum velocity or rate of enzyme catalyzed reaction

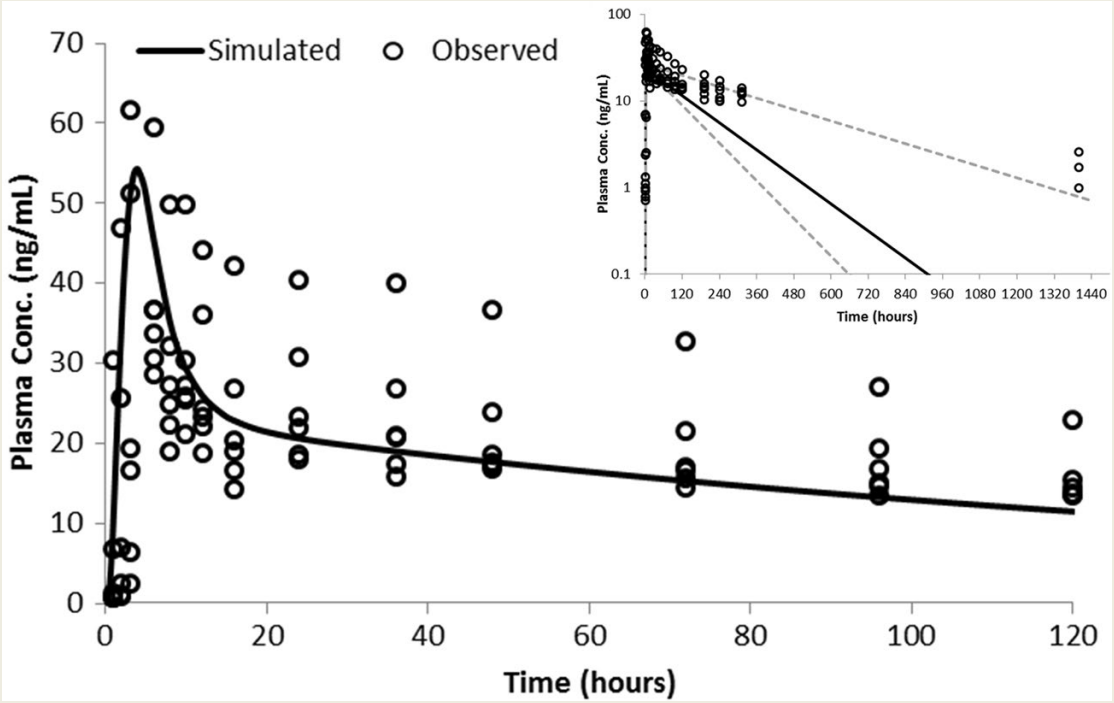
Case studies highlighting components

1. Empirical PBPK model factors from preclinical species enable First-in-Human prediction
2. Impact of blood/plasma ratio in predicting volume of distribution
3. Lipophilic weak acid with low solubility presenting a challenge to in-vitro assays
4. High molecular weight compound with expected slow passive diffusion through membranes

Empirical PBPK model factors

✓ C_{max}
✓ V_{ss}
✓ Bioavailability

Compound 1	
logP	5.2 (predicted)
Ionisation type (pKa)	Neutral
Fu_P (%)	< 0.1 in all species
Blood/plasma ratio	Human: 0.64 and Rat: 0.83
Clearance mechanism (method)	Metabolic (in-vitro data)
Solubility	Aqueous solubility < 1 µg/mL
Human Peff (cm/s × 10^{-4})	1.8 scaled from PAMPA



- Human clearance was predicted using an empirical scaling factor derived from the rat which was verified by scaling of hepatocyte intrinsic clearances measured in dog and monkey
- Optimised the dog absorption models to match exposure data for the formulations with 2 adjustments:
  1. *The percentage water in small and large intestine compartments was reduced from 40 & 10% to 10 & 0.1% respectively*
  2. *Particle size was adjusted to 1 µm for a nano-suspension and 80 µm for tablets*
- **Learning opportunity**: Systemic clearance at the lower end of the predicted range and consideration of uncertainty in clearance would have avoided a protocol amendment to adjust sampling times

Impact of blood/plasma ratio (BPR)

Compound 2		
logP	4.2	
Ionisation type (pKa)	Base: 8.96, 4.12, 2.8	
Fu_P (%)	Rat: 37 Dog: 31 Minipig: 20	Rabbit: 34 Monkey: 4 Human: 17
Blood/plasma ratio	Rat: 1.8 Dog: 1.1 Minipig: 0.9	Rabbit: 1.3 Monkey: 0.8 Human: 0.6

Species	BPR	Fu_P (%)	Observed V_{ss} (L/kg) [blood]	Observed V_{ss} (L/kg) [plasma]	GastroPlus™ predicted V_{ss} (L/kg) [plasma]	Fold error V_{ss}
Rat	1.8	37	9.1	16.4	14.7	− 1.1
Rabbit	1.3	34	8.0	10.4	7.2	− 1.4
Dog	1.1	31	8.5	9.4	5.7	− 1.6
Monkey	0.8	4	7.3	5.8	2.0	− 2.9
Minipig	0.9	20	5.0	4.5	4.9	+ 1.1
Human	0.6	17	–	2.6	3.0	+ 1.2

Note: Human pharmacokinetics were measured in plasma and GastroPlus predicts plasma pharmacokinetics; only for preclinical species where observed pharmacokinetics were measured for blood was it necessary to convert blood V_{ss} to plasma V_{ss} using species-specific BPR for comparison to GastroPlus outputs

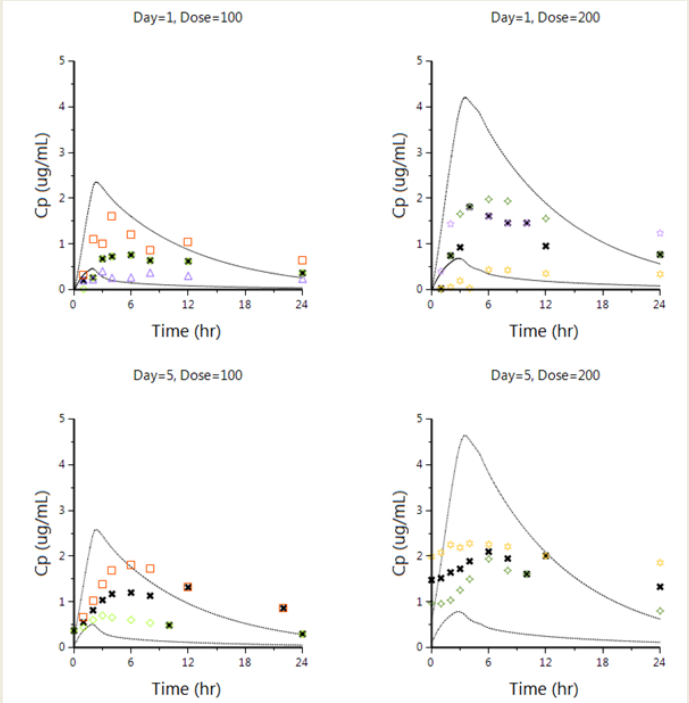
Fold error V_{ss} = − Observed V_{ss}/Predicted V_{ss} if Observed V_{ss} > Predicted V_{ss}

Fold error V_{ss} = + Predicted V_{ss}/Observed V_{ss} if Predicted V_{ss} > Observed V_{ss}

- Retrospective isolation and assessment of the impact of BPR on predicted V_{ss}
- Measured species specific BPR and Fu_p were used in each PBPK model along with measured logP and pKa values
- Lukacova method predicted the V_{ss} within 60% of the observed values in all species except monkeys, where the V_{ss} prediction error was approximately three-fold

Lipophilic weak acid with low solubility

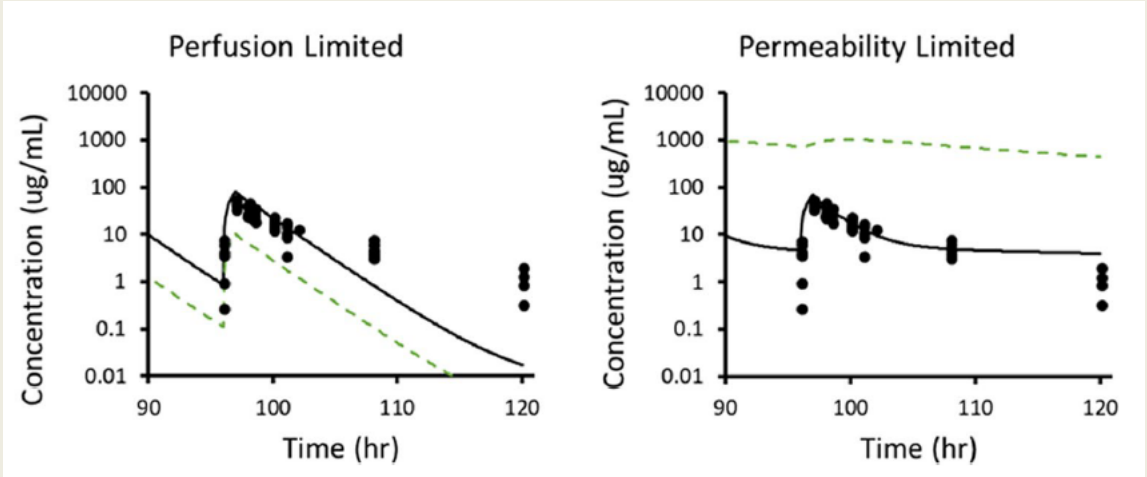
Compound 3	
logP	5.0 (predicted)
Ionisation type (pKa)	Acid: 3.4 (predicted)
Fu_P (%)	< 0.1 in all species
Blood/plasma ratio	Assumed to be 0.7 across species
Clearance mechanism (method)	Metabolic (in-vitro data)
Solubility	< 0.05 µg/mL at pH = 1
Human Peff (cm/s × 10^{-4})	3.3 (adjusted from in-vitro Data)



- Clearance and V_{ss} predictions uncertain for this compound and it seemed they were both linked to Fu_p which could not be measured
- Two combinations of parameters were explored:
  1. *Low clearance & Low V_{ss} due to a lower Fu_p*
  2. *High clearance & High V_{ss} due to a higher Fu_p*
- Assessing the in-vitro inputs against in-vivo pharmacokinetic profiles in preclinical species, and determining alternative parameters when in-vitro data were inconsistent with observed data, allowed a reasonably accurate FIH PK prediction

High molecular weight compound

Compound 4	
logP	2.48 (predicted)
Ionisation type (pKa)	Acid: 3.93, 9.73, 10.35, 11 Base: 7.87, 8.52 (predicted)
Fu_P (%)	Human: 58.5 and Rat: 46.9
Blood/plasma ratio	Human: 0.68 (predicted)
Clearance mechanism (method)	Renal (ECCS)
Solubility (predicted)	0.26 mg/mL at pH = 8.17
Human Peff (cm/s × 10^{-4})	0.0747 (predicted)



- The specific PStc (PStc per milliliter of tissue cell volume) implemented in GastroPlus was determined from PK data in the rat and subsequently used to predict the FIH PK
- Different PBPK models were explored to simulate distribution in the rat:
  1. *All perfusion-limited tissues: reasonable match to plasma but concentrations in kidney tissue were significantly under-predicted*
  2. *All permeability-limited tissues and fitting the specific PStc: matched the compound concentrations in both plasma and kidney*
- Under the assumption that cell membrane composition is similar in different species, the specific PStc value fitted against rat data was used with human physiology to accurately predict pharmacokinetics in humans

Key points

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