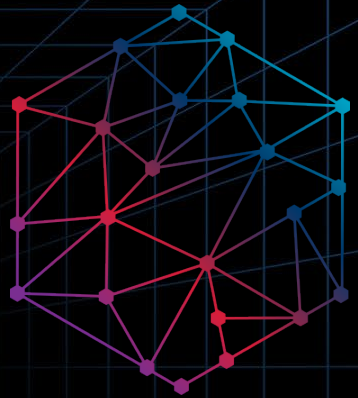
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



Confidence in FIH PBPK models

“To verify or not to verify, that is the question”

Neil Miller

SimulationsPlus

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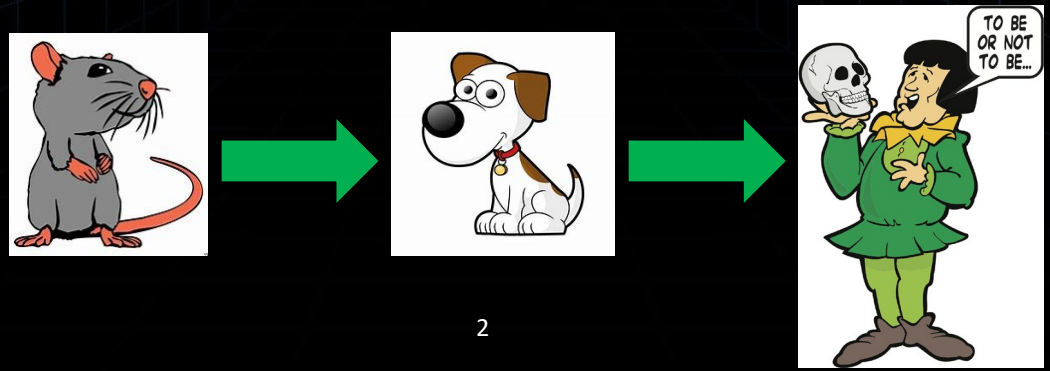
To verify or not to verify, that is the question

- “To be, or not to be, that is the question” is probably the best-known line from all drama, specifically it is from William Shakespeare's play Hamlet
- A well-known debate within the PBPK community is whether preclinical verification of a PBPK model gives more confidence in a FIH PBPK prediction…



Some comments that I have heard…

"Possibly for passive distribution, but not when transporters are involved"

"Uses all of the pieces of the jigsaw puzzle that we have available"

"Can confirm compound specific parameters"

"Helps explore mechanisms you can't predict from in vitro data"

"Could lead and inform, but not verify"

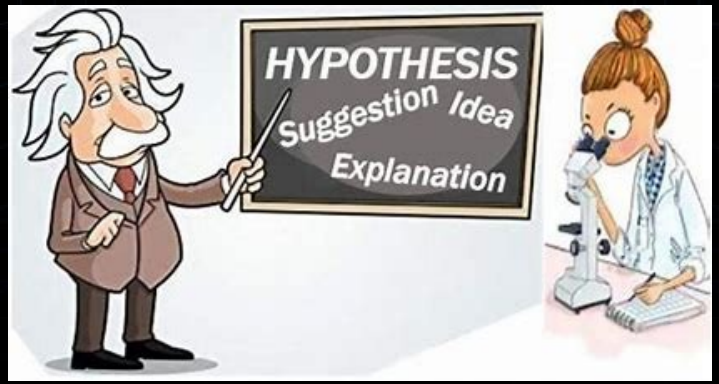
"Animal empirical adjustments may or may not work for humans"

Calling all PBPK modelers!

- We need you to be part of an industry wide experiment
- Definition of an experiment = a scientific procedure undertaken to make a discovery, test a hypothesis, or demonstrate a known fact.

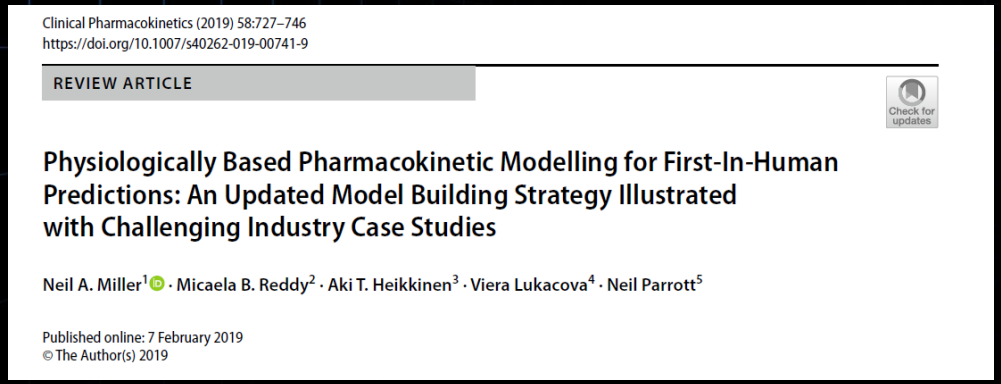
The hypothesis

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



The scientific procedure

- Thanks to the GastroPlus™ User Group we have a PBPK model building strategy to follow…



Clinical Pharmacokinetics (2019) 58:727–746
https://doi.org/10.1007/s40262-019-00741-9

REVIEW ARTICLE

Check for updates

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

Neil A. Miller[1] · Micaela B. Reddy[2] · Aki T. Heikkinen[3] · Viera Lukacova[4] · Neil Parrott[5]

Published online: 7 February 2019

GASTROPLUS® USER GROUP

- ✓ Flow diagrams for each essential component of a FIH prediction
- ✓ Thoughts illustrated with challenging industry case studies

Flow diagrams = decision trees

1. **QSPR plus PBPK assessment**: to identify the major challenges of modeling 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 before a FIH study

1. QSPR plus PBPK assessment

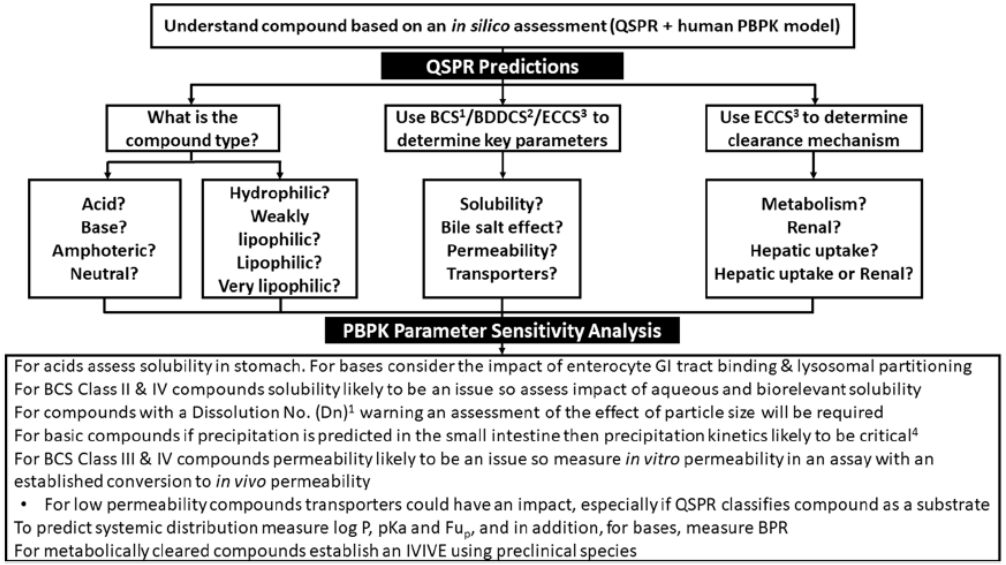


Fig. 1 Compound assessment from structure using quantitative structure–property relationship (QSPR) plus physiologically based pharmacokinetic (PBPK) modelling [27, 30–32]. *BCS* Biopharmaceutics Classification System, *BDDCS* Biopharmaceutics Drug Disposition Classification System, *BPR* blood/plasma 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]

2. Metabolism and elimination

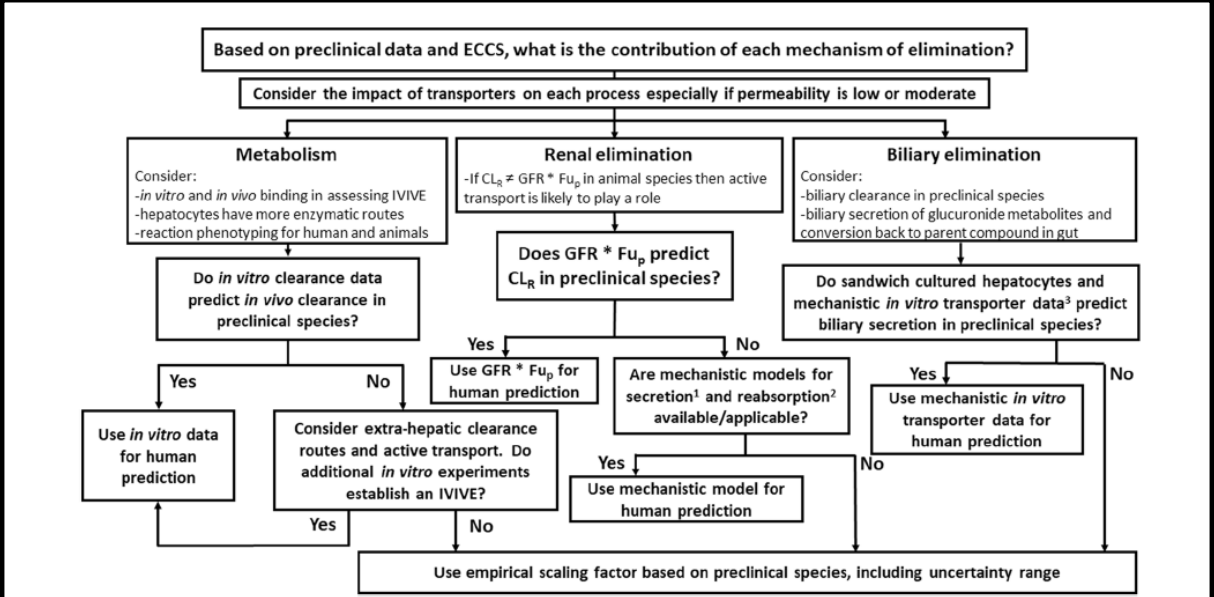


Fig. 2 Physiologically based pharmacokinetic modelling strategy for elimination [42–44]. CL_R renal clearance, $CL_{R,u}$ unbound renal clearance, *ECCS* Extended Clearance Classification System, Fu_p fraction unbound in plasma, *GFR* glomerular filtration rate, *IVIVE* in-vitro in-vivo extrapolation.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

3. Distribution

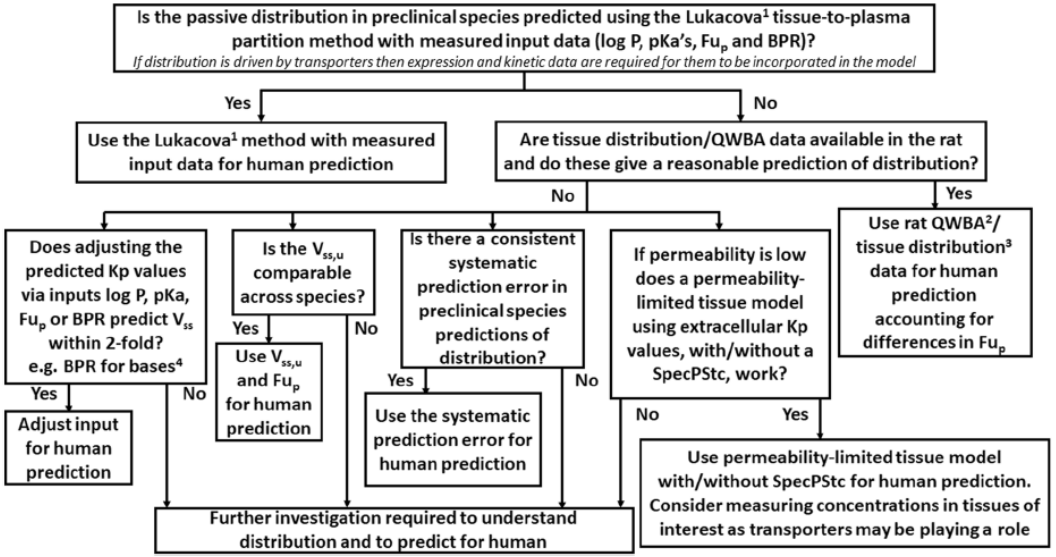


Fig. 3 Physiologically based pharmacokinetic modelling strategy for distribution [17, 50, 53, 55]. *BPR* blood/plasma ratio, Fu_p fraction unbound in plasma, K_p tissue-to-plasma partition coefficient, *SpecPStc* specific in-vivo diffusional clearance per millilitre of tissue cell volume. [1][50], [2][55],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

4. Oral absorption

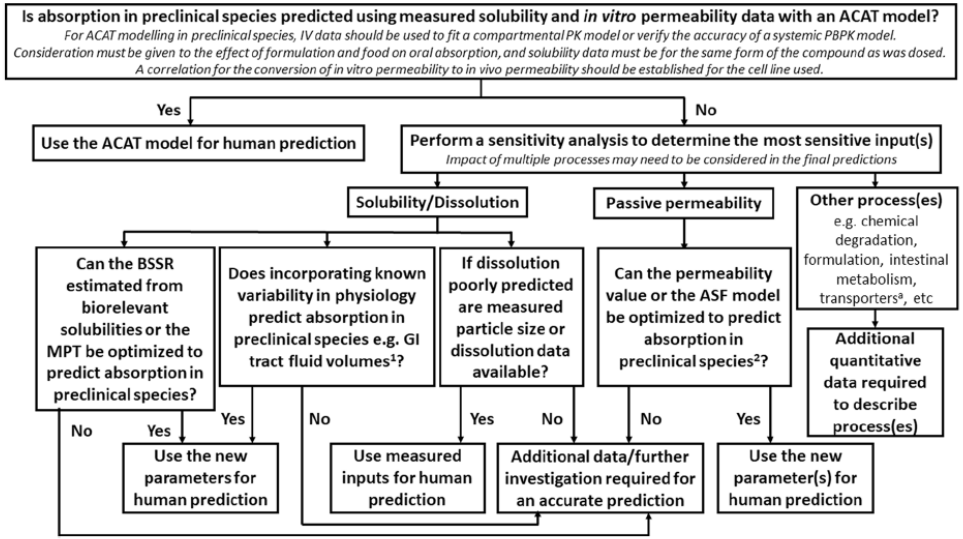


Fig. 4 Physiologically based pharmacokinetic modelling strategy for oral absorption [57, 58]. *ASF* absorption scale factors, *BSSR* bile salt solubilisation ratio, *MPT* mean precipitation time. [a] Other processes" transporters: efflux transporters can be incorporated in GastroPlus models with a simple 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]

5. Gut wall metabolism

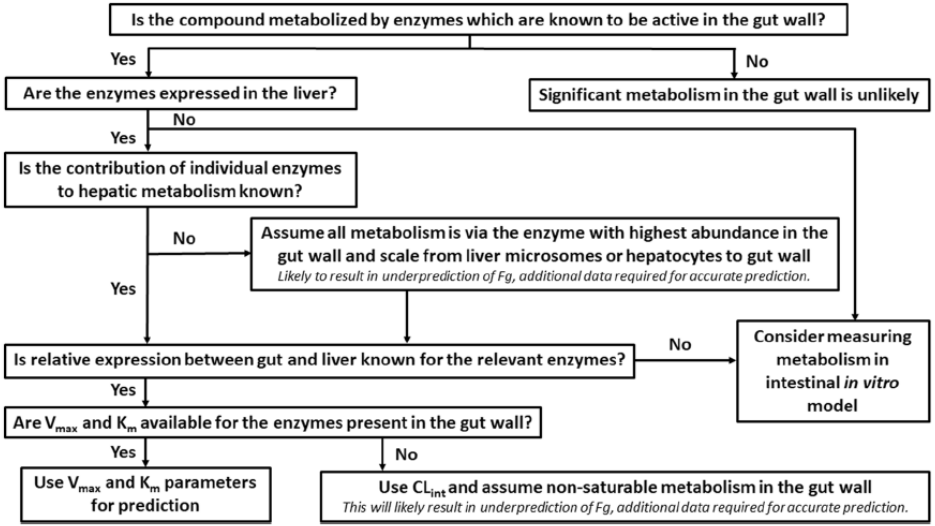


Fig. 5 Physiologically based pharmacokinetic modelling strategy for assessing gut wall metabolism [65]. CL_{int} hepatic intrinsic clearance, Fg fraction of drug escaping gut wall metabolism, K_m concentration of substrate at half V_{max}, V_{max} maximum velocity or rate of enzyme catalyzed reaction.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

6. Uncertainty and variability analyses

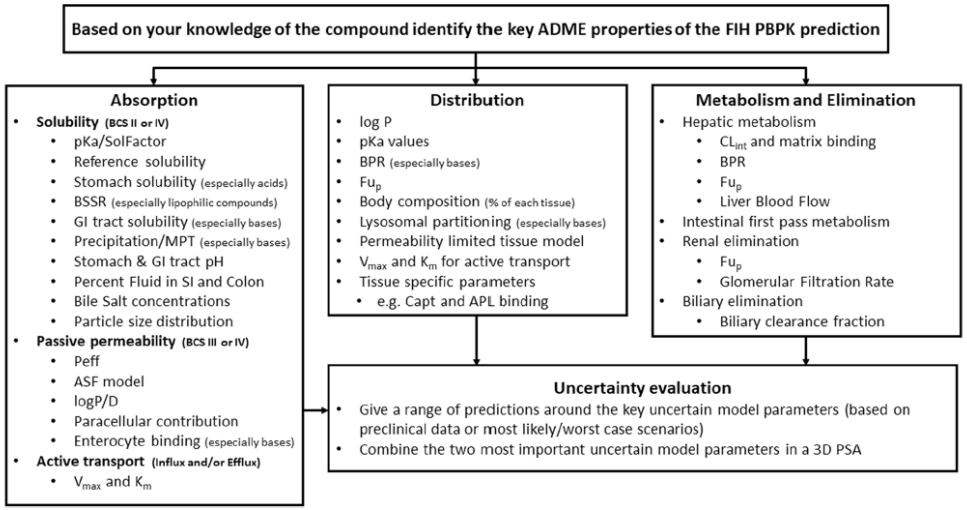
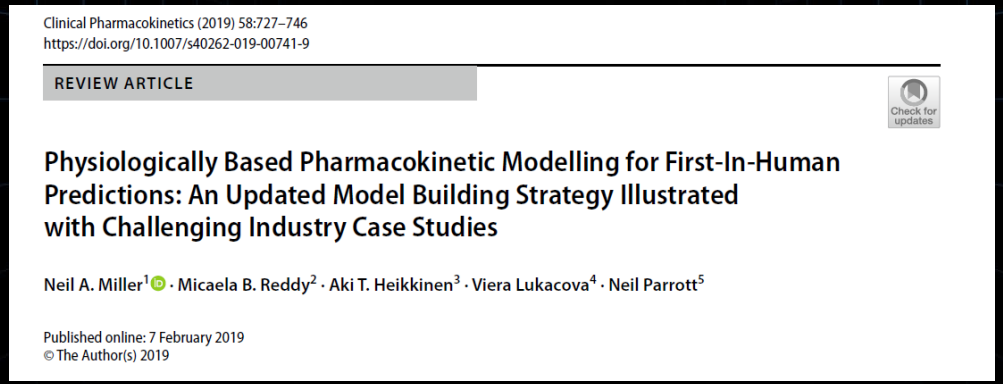


Fig. 6 Physiologically based pharmacokinetic modelling strategy for a potentially useful parameter sensitivity analysis (PSA) to be driven by the molecule properties and uncertainty evaluation. *3D* three-dimensional, *ADME* Absorption, Distribution, Metabolism and Excretion, *APL* acidic phospholipid, *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

Read the case studies in the publication

- Available as open access in Clinical Pharmacokinetics



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Q&A

Questions & Answers

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