Model-Informed Drug Development

2021 Virtual Conference

Confidence in FIH PBPK models "To verify or not to verify, that is the question"

Neil Miller



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"

"Can confirm compound specific parameters"

"Could lead and inform, but not verify"

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

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

"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.

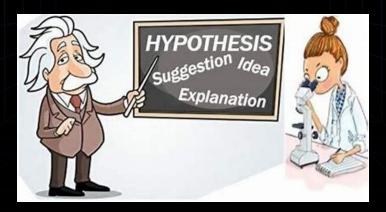






The hypothesis

 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...

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





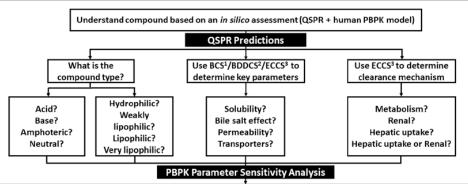
Flow diagrams = decision trees

- 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



For acids assess solubility in stomach. For bases consider the impact of enterocyte GI tract binding & lysosomal partitioning For BCS Class II & IV compounds solubility likely to be an issue so assess impact of aqueous and biorelevant solubility For compounds with a Dissolution No. (Dn)1 warning an assessment of the effect of particle size will be required For basic compounds if precipitation is predicted in the small intestine then precipitation kinetics likely to be critical⁴ For BCS Class III & IV compounds permeability likely to be an issue so measure in vitro permeability in an assay with an established conversion to in vivo permeability

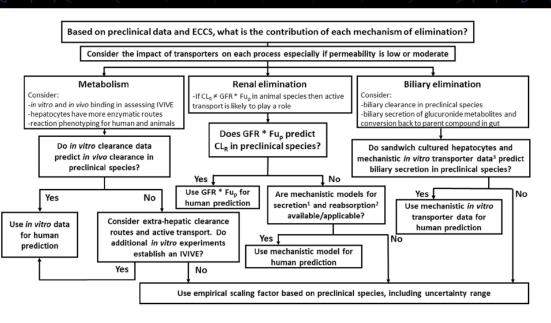
· For low permeability compounds transporters could have an impact, especially if QSPR classifies compound as a substrate To predict systemic distribution measure log P, pKa and Fu_p, and in addition, for bases, measure BPR For metabolically cleared compounds establish an IVIVE using preclinical species

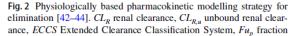
Fig. 1 Compound assessment from structure using quantitative structure-property relationship (QSPR) plus physiologically based pharmacokinetic (PBPK) modelling [27, 30-32]. BCS Biopharmaceutics Classification System, BDDCS Biopharmaceutics Drug Disposition Classification System, BPR blood/plasma ratio,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

ber (the ratio of small intestine transit time/idealised dissolution time), ECCS Extended Clearance Classification System, Fu_n Fraction unbound in plasma, GI gastrointestinal, IVIVE in-vitro in-vivo extrapolation. ¹[27], ²[31], ³[30], ⁴[32]



2. Metabolism and elimination

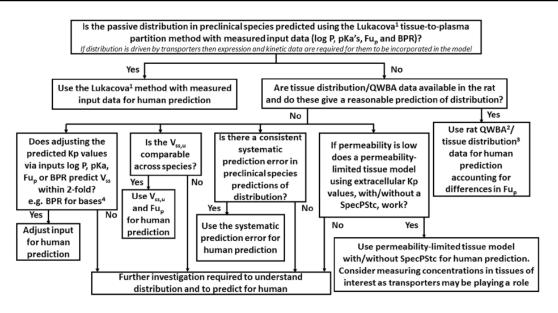




unbound in plasma, GFR glomerular filtration rate, IVIVE in-vitro in-vivo extrapolation. $^{1}[42], ^{2}[43], ^{3}[44]$



3. Distribution





Stc specific in-vivo diffusional clearance per millilitre of tissue cell volume. $^1[50], ^2[55], ^3[17], ^4[53]$



4. Oral absorption

Is absorption in preclinical species predicted using measured solubility and *in vitro* permeability data with an ACAT model?

For ACAT modelling in preclinical species, IV data should be used to fit a compartmental PK model or verify the accuracy of a systemic PBPK model.

Consideration must be given to the effect of formulation and food on oral absorption, and solubility data must be for the same form of the compound as was dosed.

A correlation for the conversion of in vitro permeability to in vivo permeability should be established for the cell line used.

Use the ACAT model for human prediction Perform a sensitivity analysis to determine the most sensitive input(s) Impact of multiple processes may need to be considered in the final predictions Solubility/Dissolution Passive permeability Other process(es) e.g. chemical degradation, Can the BSSR If dissolution formulation, intestinal Does incorporating known Can the permeability metabolism. poorly predicted estimated from variability in physiology value or the ASF model transportersa, etc biorelevant are measured be optimized to predict predict absorption in solubilities or the particle size or preclinical species e.g. GI absorption in Additional MPT be optimized to dissolution data tract fluid volumes1? preclinical species²? quantitative predict absorption in available? data required preclinical species? to describe

Yes

Use measured

inputs for human

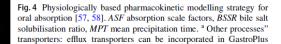
prediction

No

Additional data/further

investigation required for

an accurate prediction



Use the new

parameters for

human prediction

No

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]

Yes

Use the new

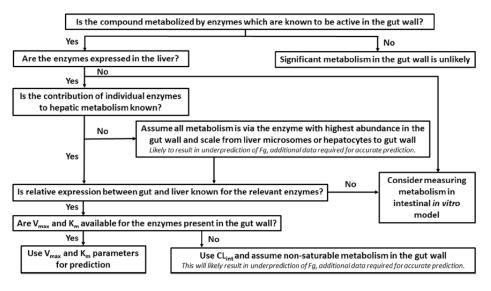
parameter(s) for

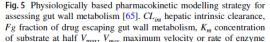
human prediction

process(es)



5. Gut wall metabolism





catalyzed reaction. Note: Gut wall metabolism is often saturable, and thus if $V_{\rm max}$ and $K_{\rm m}$ parameters are available, evaluate saturation relative to dose



6. Uncertainty and variability analyses

Based on your knowledge of the compound identify the key ADME properties of the FIH PBPK prediction Absorption Distribution Metabolism and Elimination Solubility (BCS II or IV) log P Hepatic metabolism pKa/SolFactor pKa values CL_{int} and matrix binding · Reference solubility BPR (especially bases) BPR Stomach solubility (especially acids) Fu. Fu_n Liver Blood Flow BSSR (especially lipophilic compounds) Body composition (% of each tissue) GI tract solubility (especially bases) Lysosomal partitioning (especially bases) Intestinal first pass metabolism Permeability limited tissue model Renal elimination Precipitation/MPT (especially bases) · Stomach & GI tract pH V_{max} and K_m for active transport Tissue specific parameters Percent Fluid in SI and Colon Glomerular Filtration Rate Bile Salt concentrations · e.g. Capt and APL binding Biliary elimination Particle size distribution · Biliary clearance fraction Passive permeability (BCS III or IV) Peff ASF model **Uncertainty evaluation** logP/D Give a range of predictions around the key uncertain model parameters (based on Paracellular contribution preclinical data or most likely/worst case scenarios) Enterocyte binding (especially bases) Combine the two most important uncertain model parameters in a 3D PSA Active transport (Influx and/or Efflux) V_{max} and K_m



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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