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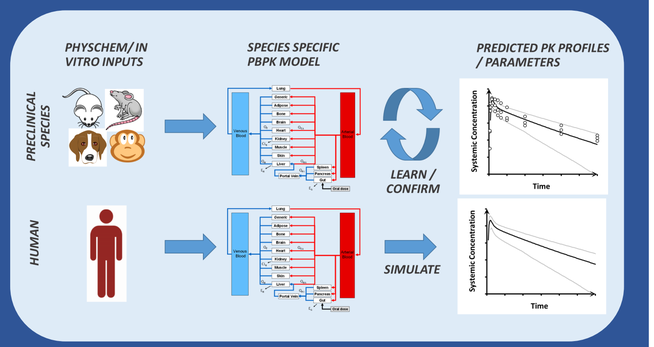
PBPK APPLICATION IN DRUG DISCOVERY AND DEVELOPMENT

Real-World Application of Physiologically Based Pharmacokinetic Modeling (PBPK) in Support of Decision-Making During Drug Discovery; Guidance and Recommendations for the Utility of PBPK Impact on Candidate Selection and Human Pharmacokinetic Prediction Through Case Examples

STATEMENT OF PURPOSE

PBPK models may be developed and applied during drug discovery to assist in decision making.



PBPK MODELING STRATEGY FOR FIH SIMULATIONS

Distribution (V_{SS} and Profile Shape)

- Physchem and compound class influence tissue composition model selection
- Incorporation of Kp scalars
- Passive versus active transport
- Comparison with scaling from animals

Clearance (t ½ and Extraction Ratio)

- Clearance mechanism and BDDCS classification
- IVIVC across species and use of empirical scaling factors
- Involvement of transporters
- Linearity of clearance
- Comparison with scaling from animals

Absorption (fa, ka)

- BCS classification
- Passive versus active permeability
- Solubility across pH in buffer versus simulated intestinal media
- Linearity of absorption
- Formulation type
- Comparison with scaling from animals

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Case Study 1

- A PBPK model was developed to identify the most promising candidates, from available compounds in a chemical series, for further studies in human subjects.
- The goal of this discovery program was to develop a compound with decreased clearance, relative to an approved drug, to improve on the current dosing regimen.

Distribution Modelling

- V_{ss} predicted
- Kp scalar to recover observed V_{ss}

Absorption Modelling

- mechanistic ADAM model to describe drug absorption
- MechPeff Model to determine $P_{trans,0}$
- high solubility compound was treated as solution formulation

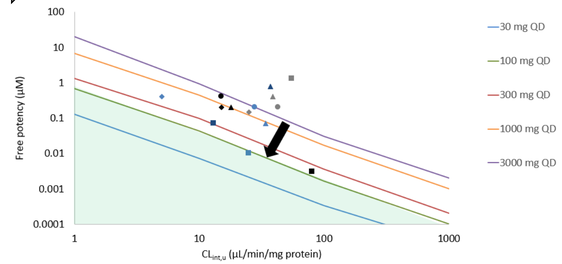
Clearance IVIVE Exploration

- CL extrapolated using intrinsic clearance (CL_{int}) from liver microsomes along with empirical scalar to account for clinical CL underprediction

Human Predictions

- verified model was then applied across all other compounds in the chemical series for candidate selection
- physchem and *in vitro* inputs for each compound.
- target exposure based on EC_{90}

Heatmap based on free potency versus unbound intrinsic clearance for all compounds.

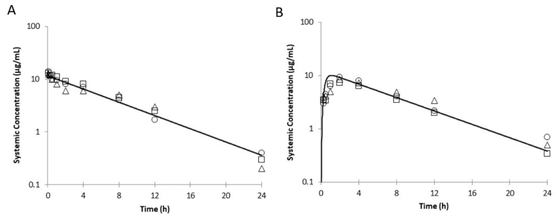


Individual compounds in the series summarized as points, relative to the approved compound (black diamond). The green shaded region indicates the optimal region of target potency/clearance resulting in lower dose requirements. The black arrow indicates improvements required for non-optimal candidates.

Case Study 2

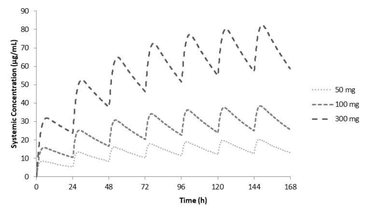
- PBPK modelling was used to predict human PK following oral absorption.
- In addition, the effect of CYP3A4 auto-inactivation and drug-drug interaction (DDI) liability as a perpetrator was investigated.

Simulated and observed concentration-time plots following 1 mg/kg IV (A) and 1 mg/Kg PO (B) in rat.



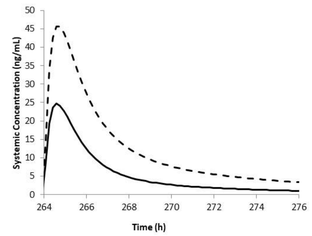
The solid line represents the mean of the simulated concentration-time profiles. Open circles squares and triangles represent individual observed data points (n=3 Sprague-Dawley rats).

Simulated mean human PO PK profile (tablet) for 50 – 300 mg QD using HH CL_{int} as CL input into the model.



Simulated trial design includes 10 trials of n=10 healthy subjects, aged 20 – 50 with 50% females.

Simulated midazolam mean plasma concentration-time profiles in the absence (solid line) or presence (dashed line) of inhibitor

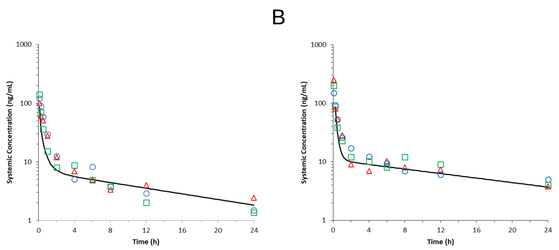


Simulated trial design includes 10 trials of n=10 healthy subjects, aged 20 – 50 with 50% females.

Case Study 3

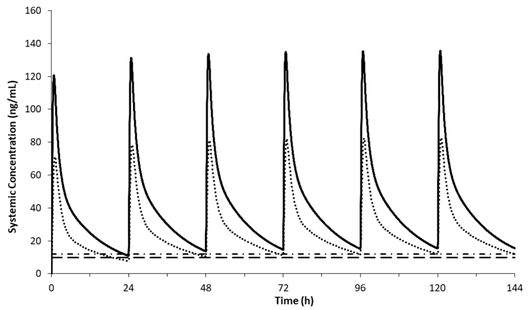
- The PBPK modeling approach and assumptions were first verified in preclinical species (rats, dogs, and monkeys) for both parent and metabolite
- After verification of the preclinical species PBPK models, a human PBPK model was developed for the prediction of parent and metabolite PK simultaneously after oral administration

Simulated and observed IV concentration-time plots of parent (A) and metabolite (B) after 1 mg/kg dose in the rat using Method 3 predicted Kp and Vss and the measured IV CL as input into the model.



The solid line represents the mean of the simulated concentration-time profiles. Open circles, squares and triangles represent mean observed data points from a study in n=3 animals.

Simulated human PO PK profile for Compound and its metabolite at 500 mg QD.



The solid line and dotted lines represent the mean of parent and metabolite; dashed straight lines represent the EC90 values of parent and active metabolite, respectively.

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