



Application of Physiologically Based Modeling in Pre-clinical to Clinical PK/PD Prediction



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Basel



Outline

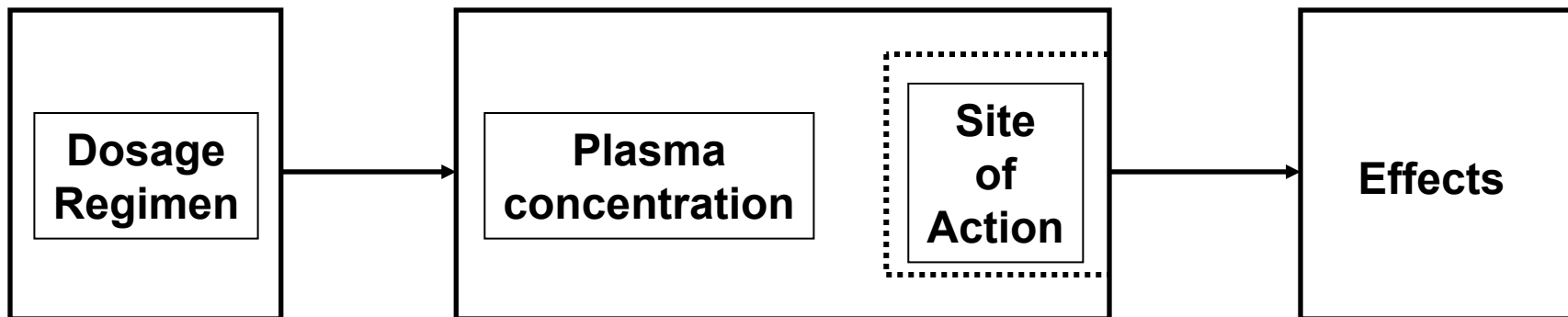
1. Why predict pharmacokinetics?
2. Why use physiologically based pharmacokinetic models?
3. Validation of the models
4. Some examples
5. Areas for future development

PK and PD



Pharmacokinetics

Pharmacodynamics



Adapted from Rowland and Tozer 2nd Ed.

Traditional pharmacokinetic models

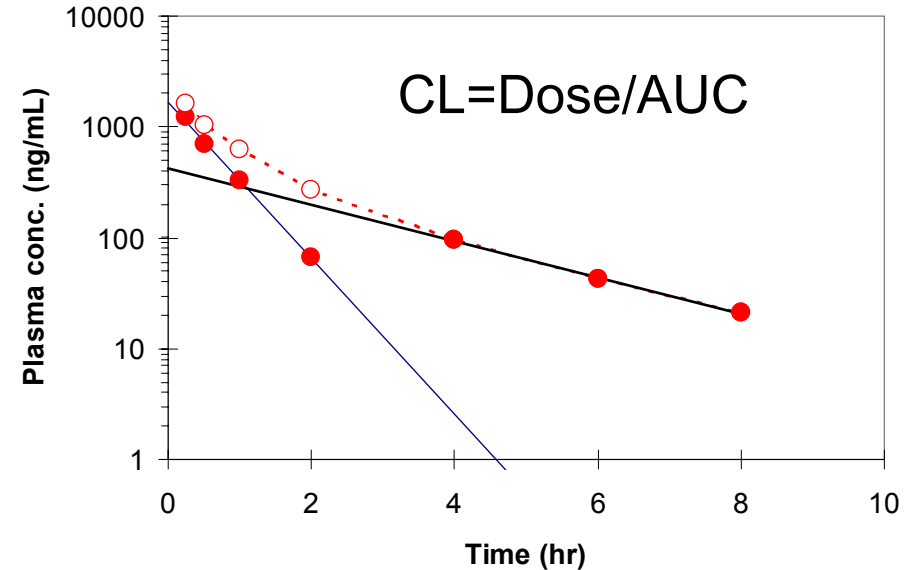


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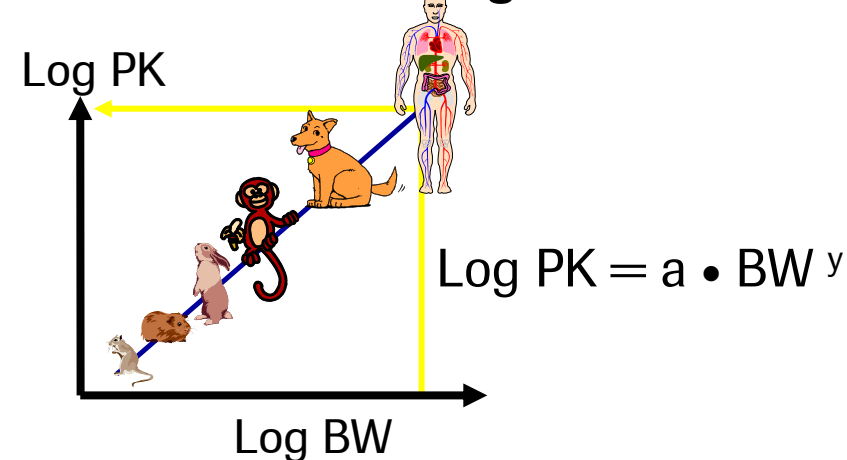
- In vivo experiment in animals
- Fit an empirical model to the concentration profiles or perform model independent analysis to derive parameters (CL, V, $T_{1/2}$)

Then,

- For QSPR use correlation analysis of PK parameters to compound properties
- For prediction between species use empiric approaches e.g. allometry



Allometric scaling



Physiologically based pharmacokinetic models (PBPK)



A whole body PBPK model for drug disposition

Input parameters

Compound specific

LogP

pKa

Intrinsic clearance

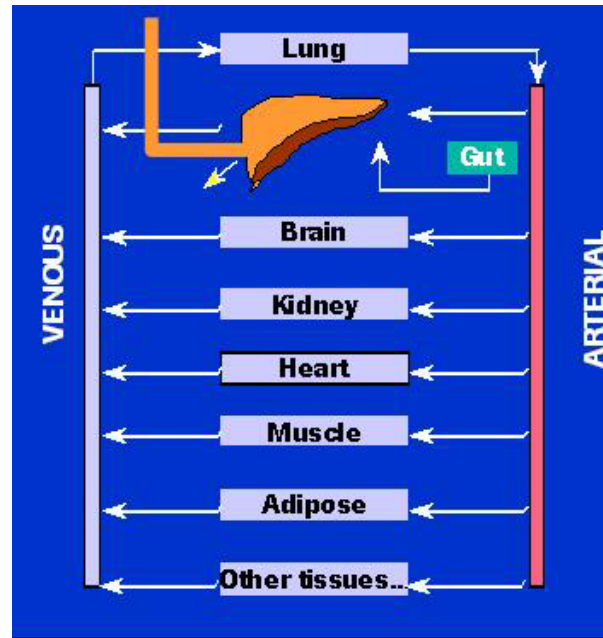
Protein binding

Species specific

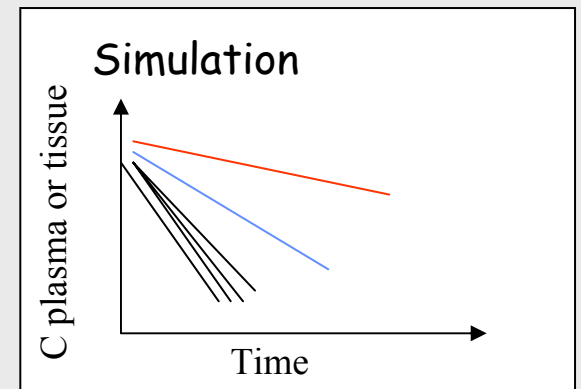
Blood flow

Tissue volume

Tissue composition



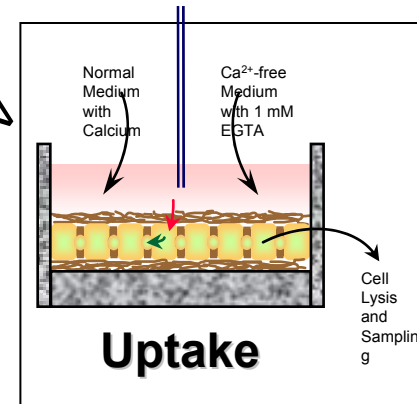
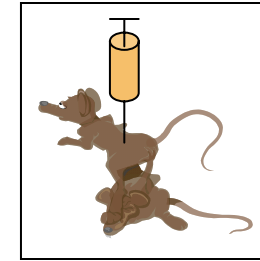
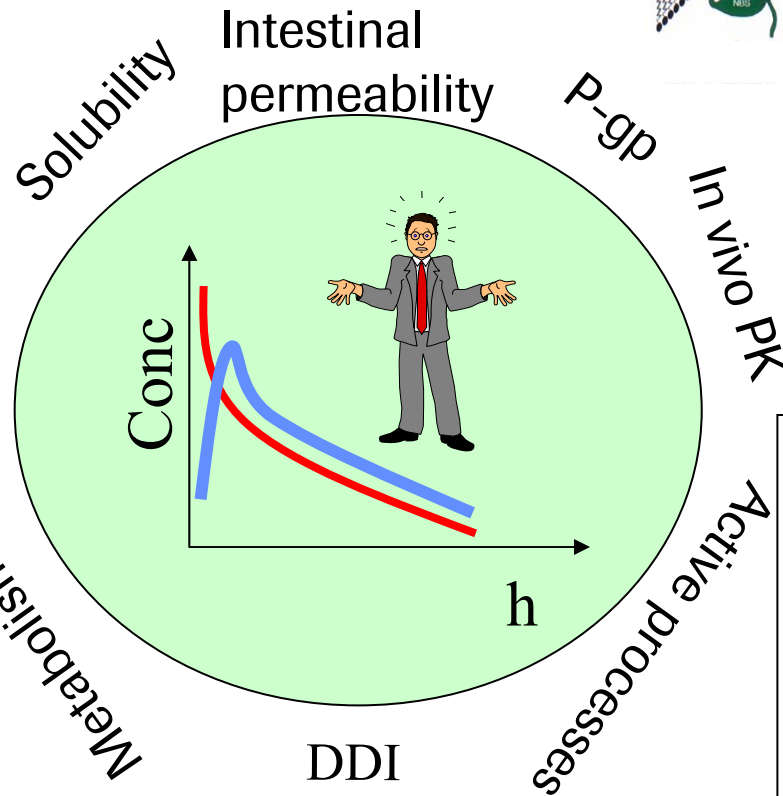
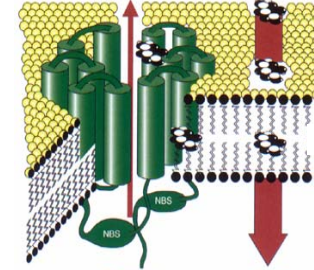
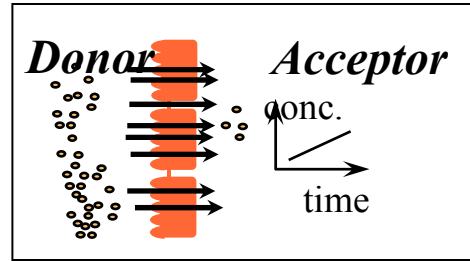
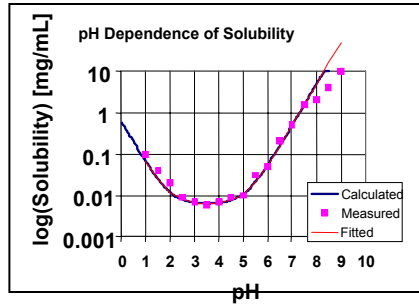
Output



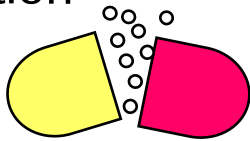
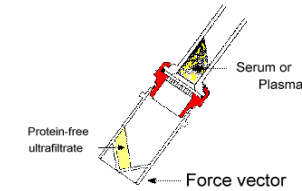
PBPK advantages, data integration



In silico estimates



formulation

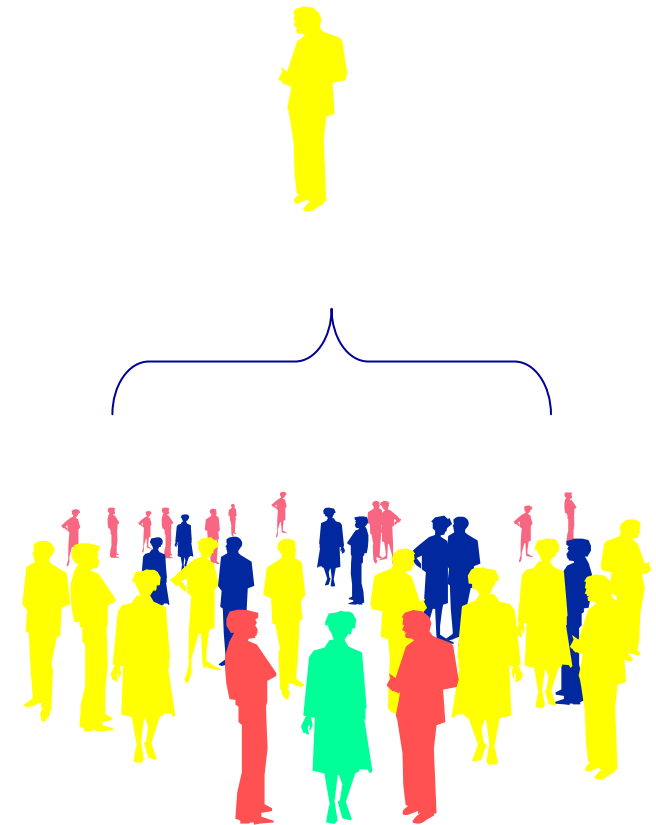


BFC (at Km) \longrightarrow dealkylated met (fluorescent)
 IC_{50}, K_i

PBPK advantages, model flexibility



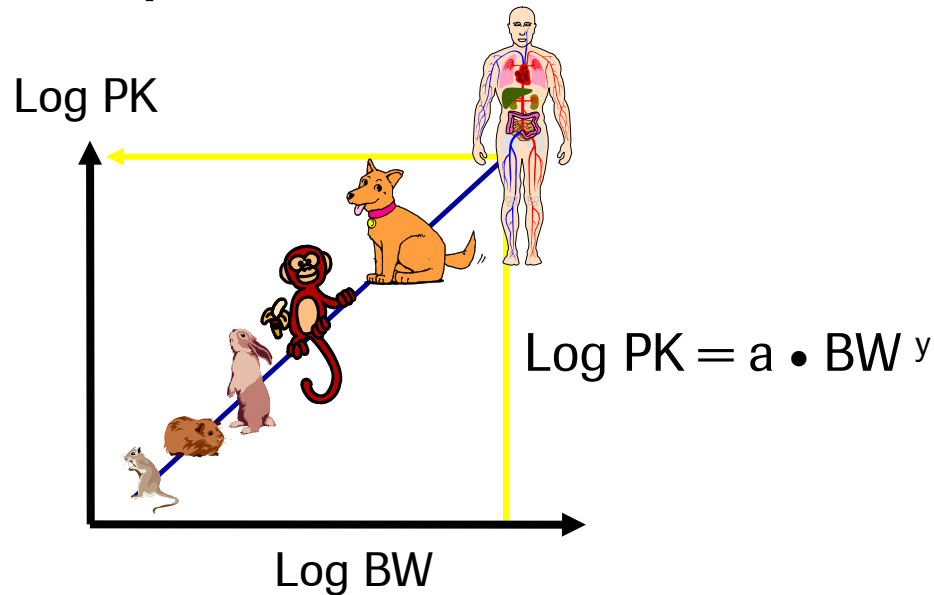
	Absorption	Clearance	Distribution
Generic	HT solubility PAMPA or in silico Peff	Liver microsomes Well stirred model LM Binding in silico	Tissue composition Perfusion limited
Refined	Fessif / fassif solubility Caco2 permeability Gut metabolism Efflux / Influx transport GI fluid degradation Formulation effects	Hepatocytes Renal clearance Biliary excretion Transport processes Intestinal metabolism Binding (plasma, liver)	Permeability limited Measured Kp In vivo Vss Transport



PBPK advantages, predictive power

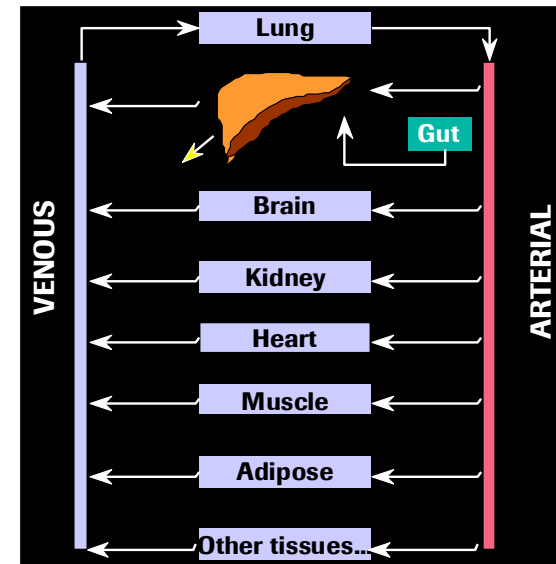


Empirical Methods



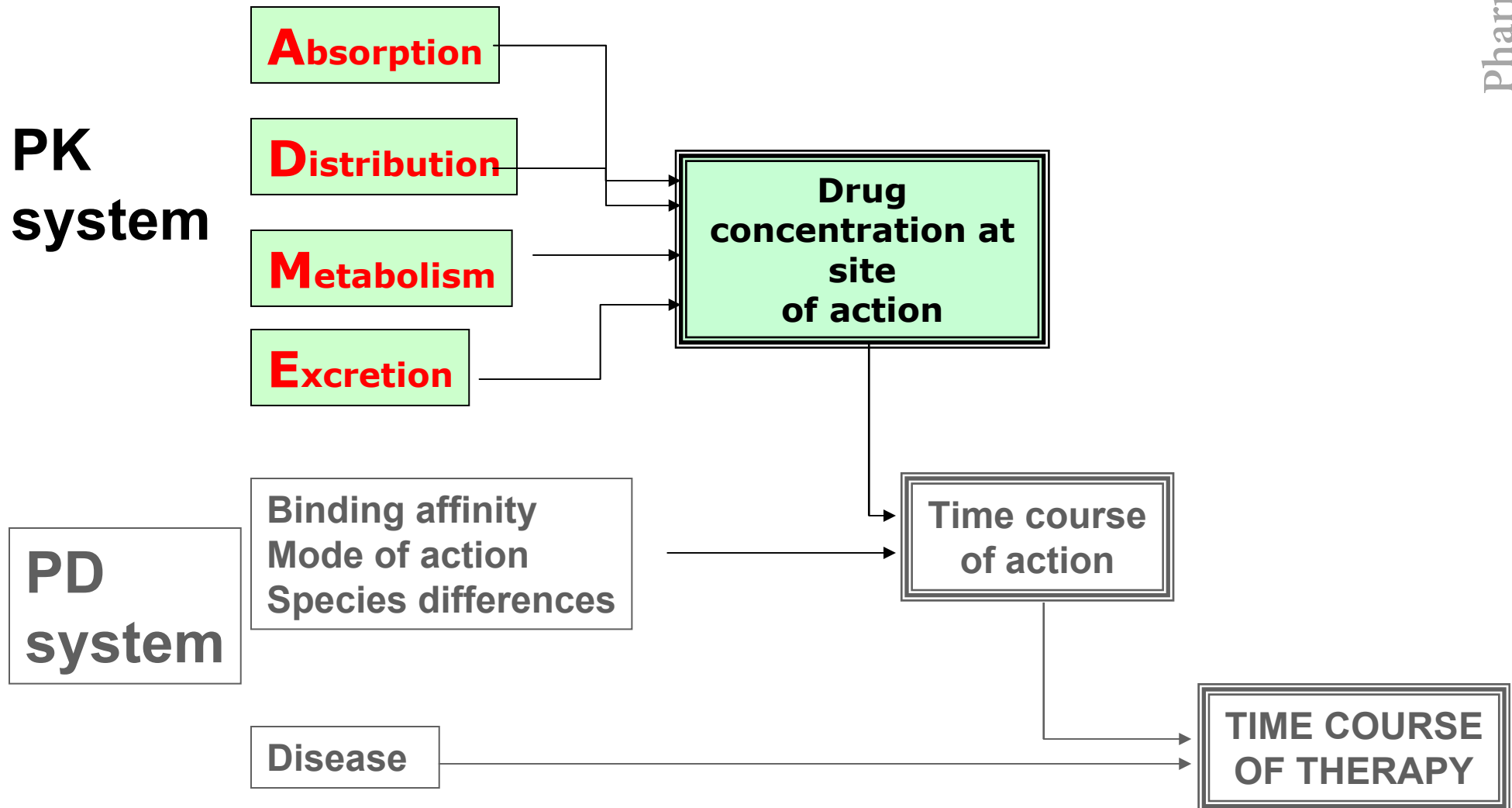
- + simple
- frequently inaccurate
- predict average parameters
- predict only parent compound
- data intensive (in vivo PK)

PBPK



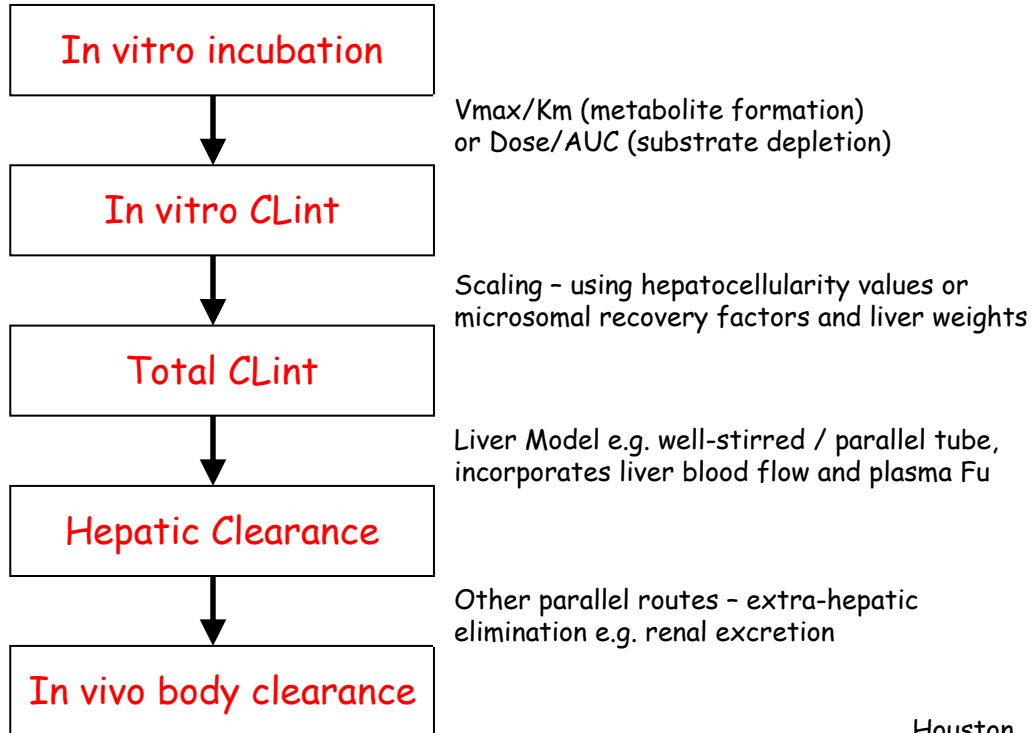
- +/- more sophisticated
- Need training for use
- + consider variability and uncertainty
- + predict full profiles
- + potential to predict metabolites

PBPK models for key processes



PBPK, models for elimination

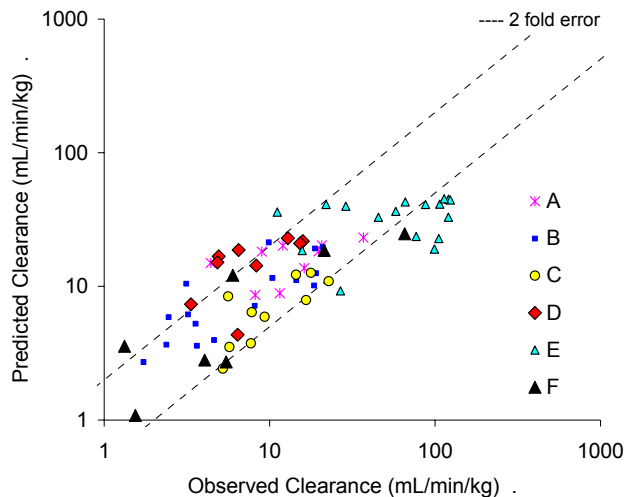
Physiological scaling of hepatic metabolic clearance



Houston, 1994

PBPK, models for clearance

Physiological scaling of hepatic metabolic clearance from screening data



Roche data for predictions in rat

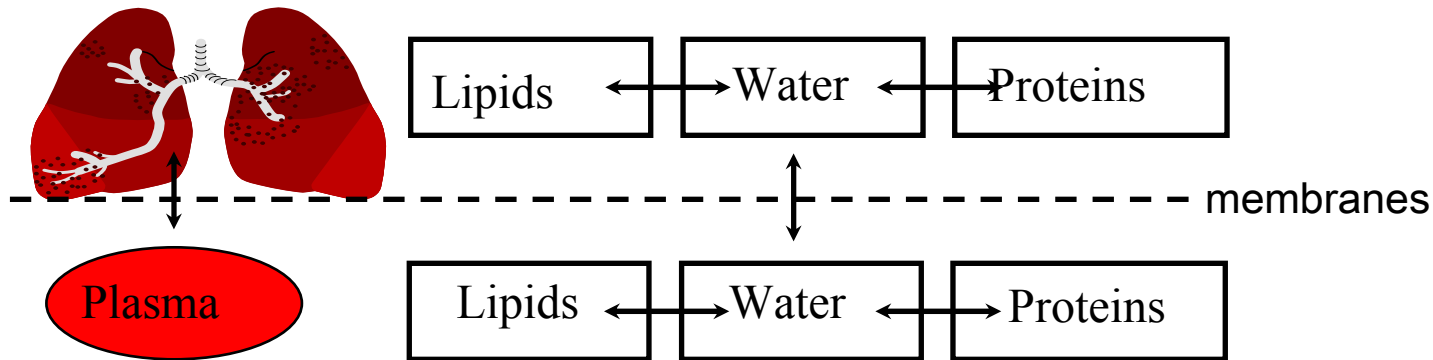
PARROTT, N., N. PAQUEREAU, et al. (2005). "An Evaluation of the Utility of Physiologically Based Models of Pharmacokinetics in Early Drug Discovery." Journal of Pharmaceutical Sciences **94**(10): 2327-2343.

For more details of validation of clearance predictions in human and recent advances see. WWW.SIMCYP.COM

Rostami-Hodjegan, A. and G. T. Tucker (2007). "Simulation and prediction of in vivo drug metabolism in human populations from in vitro data." NATURE REVIEWS DRUG DISCOVERY **6**: 141-148.

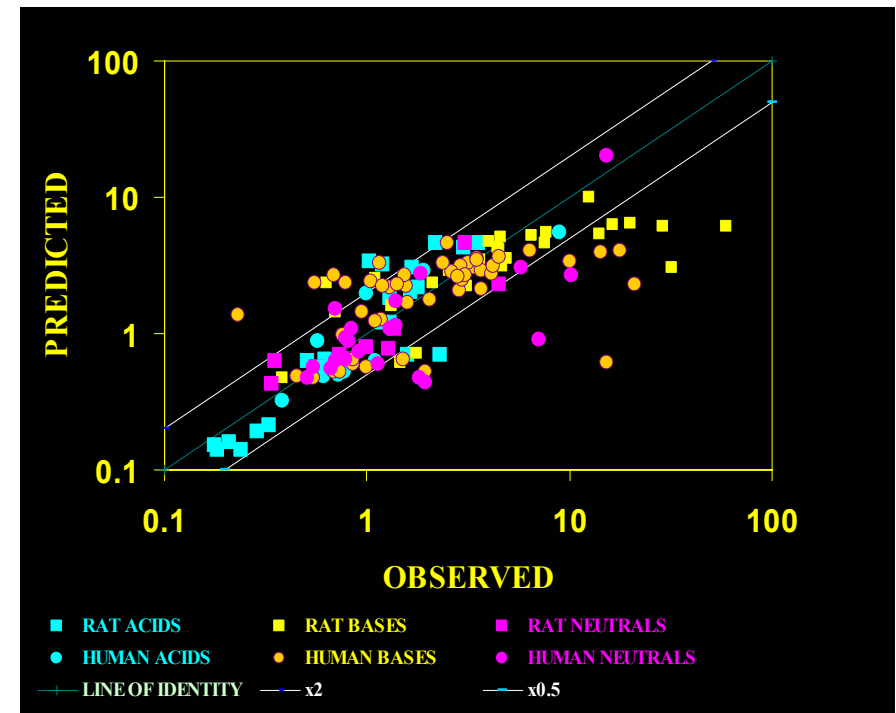
PBPK, models for distribution

Mechanistic models of drug distribution



- V_{ss} (L/Kg) predicted from tissue volumes and drug tissue-plasma partition coefficients, K_p of 123 drugs.
- Tissue K_p values predicted from plasma binding, pK_a , $\log P$ octanol/buffer and $\log D$ olive oil/buffer.

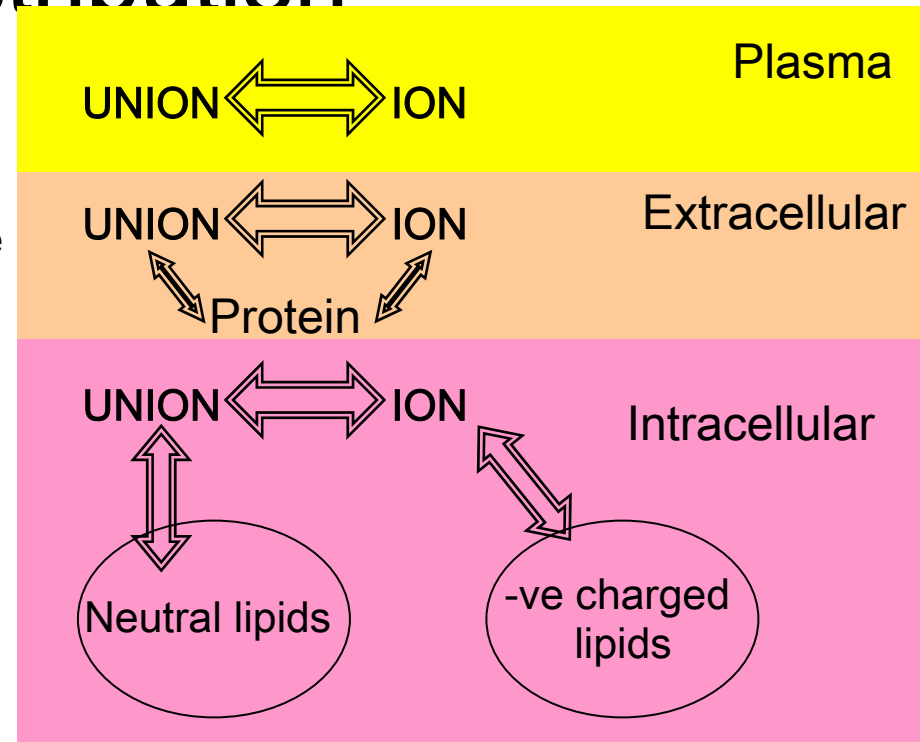
Poulin, P. and F. Theil (2002). "Prediction of pharmacokinetics prior to in vivo studies I. Mechanism-based prediction of volume of distribution." *J. Pharm. Sci.* 91: 129-156.



PBPK, models for distribution

Recent papers from Rodgers and Rowland extend and improve models

- Strong bases bind to -ve charged membrane phospholipids
- Drug ionization accounted for
- Extracellular protein binding accounted for
- Acids, neutrals, zwitterions and weak bases
81% predicted within 3-fold
- 89% of strong bases within 3-fold

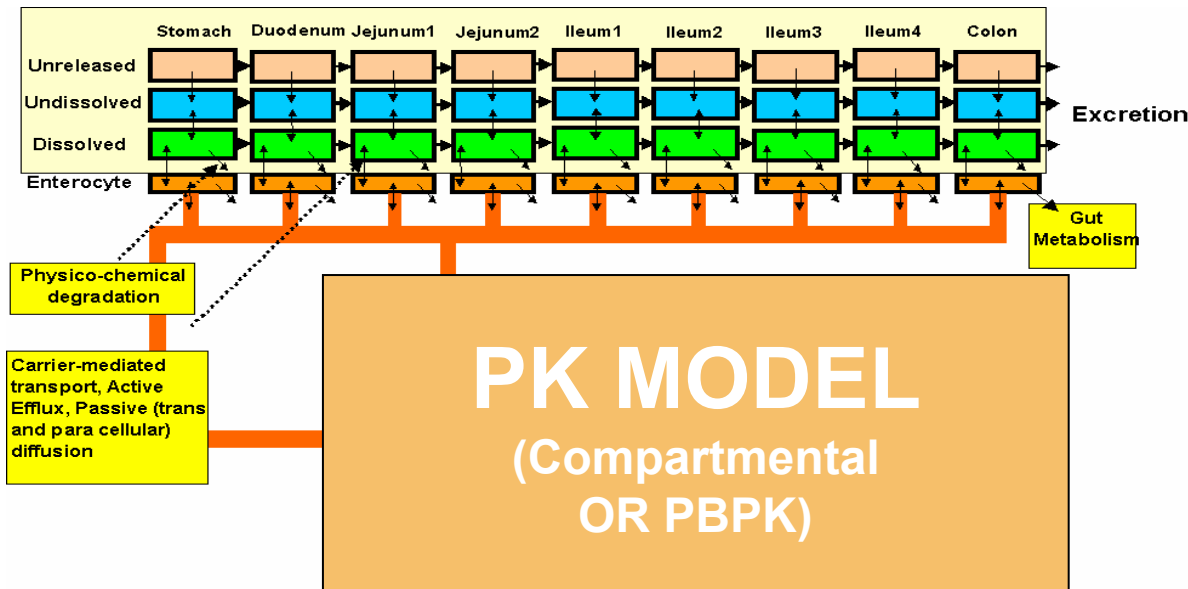


For details of recent advances see.

RODGERS, T. and M. ROWLAND (2006). "Physiologically Based Pharmacokinetic Modelling 2: Predicting the Tissue Distribution of Acids, Very Weak Bases, Neutrals and Zwitterions." JOURNAL OF PHARMACEUTICAL SCIENCES 95(6): 1238-1257.

PBPK, absorption models

e.g. Advanced Compartmental Absorption and Transit model



Agoram, B., W. S. Woltosz, et al. (2001). "Predicting the impact of physiological and biochemical processes on oral drug bioavailability." *Adv. Drug Deliv. Rev.* 50(Supplement 1): S41–S67.

Prediction of intestinal absorption: comparative assessment of GASTROPLUS (TM) and IDEA (TM). Parrott N, Lave T. *Eur J Pharm Sci* 17 (1-2): 51-61 OCT 2002

Predicting pharmacokinetic food effects using biorelevant solubility media and physiologically based modeling. Jones HM, Parrott N, Ohlenbusch G, Lave T. *Clin Pharmacokinet* 45 (12): 1213-1226 2006

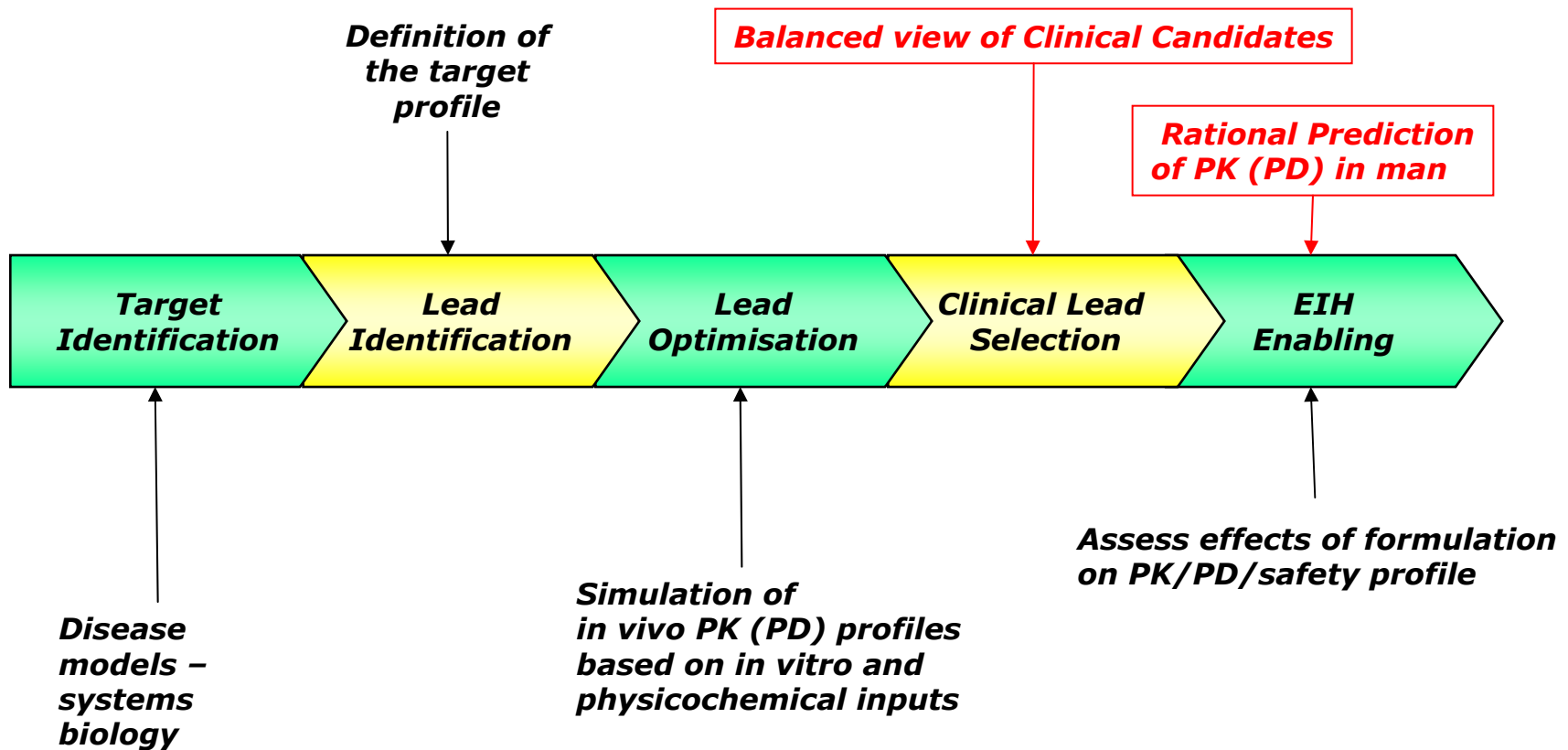
A strategy for preclinical formulation development using GastroPlus (TM) as pharmacokinetic simulation tool and a statistical screening design applied to a dog study. Kuentz M, Nick S, Parrott N, Rothlisberger D. *Eur J Pharm Sci* 27 (1): 91-99 JAN 2006



Examples of PBPK use in Roche

1. Prediction of human pharmacokinetics for entries into clinical development
2. Data integration and compound comparison during clinical candidate selection

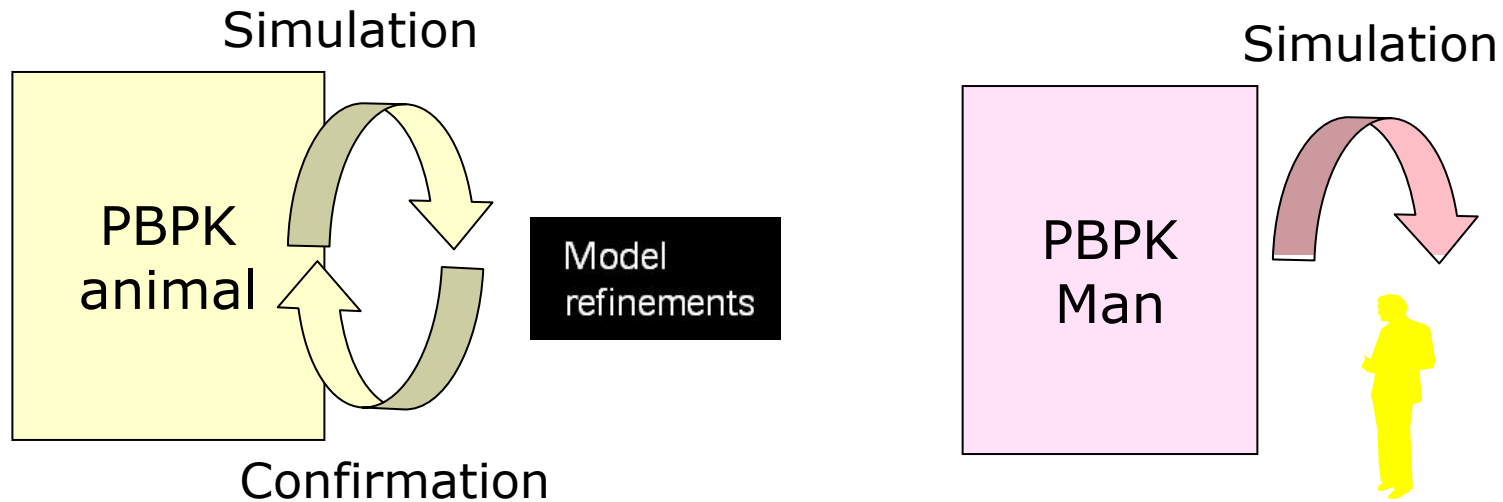
Impact of PK prediction during discovery and non-clinical development



PBPK, predictions in human

Hannah Jones, Neil Parrott, Karin Jorga, Thierry Lave. (2006). "A Novel Strategy for Physiologically Based Predictions of Human Pharmacokinetics." Clin Pharmacokinet 45(5).

Molecular descriptors; in vitro and in silico data ADME / PD / Tox

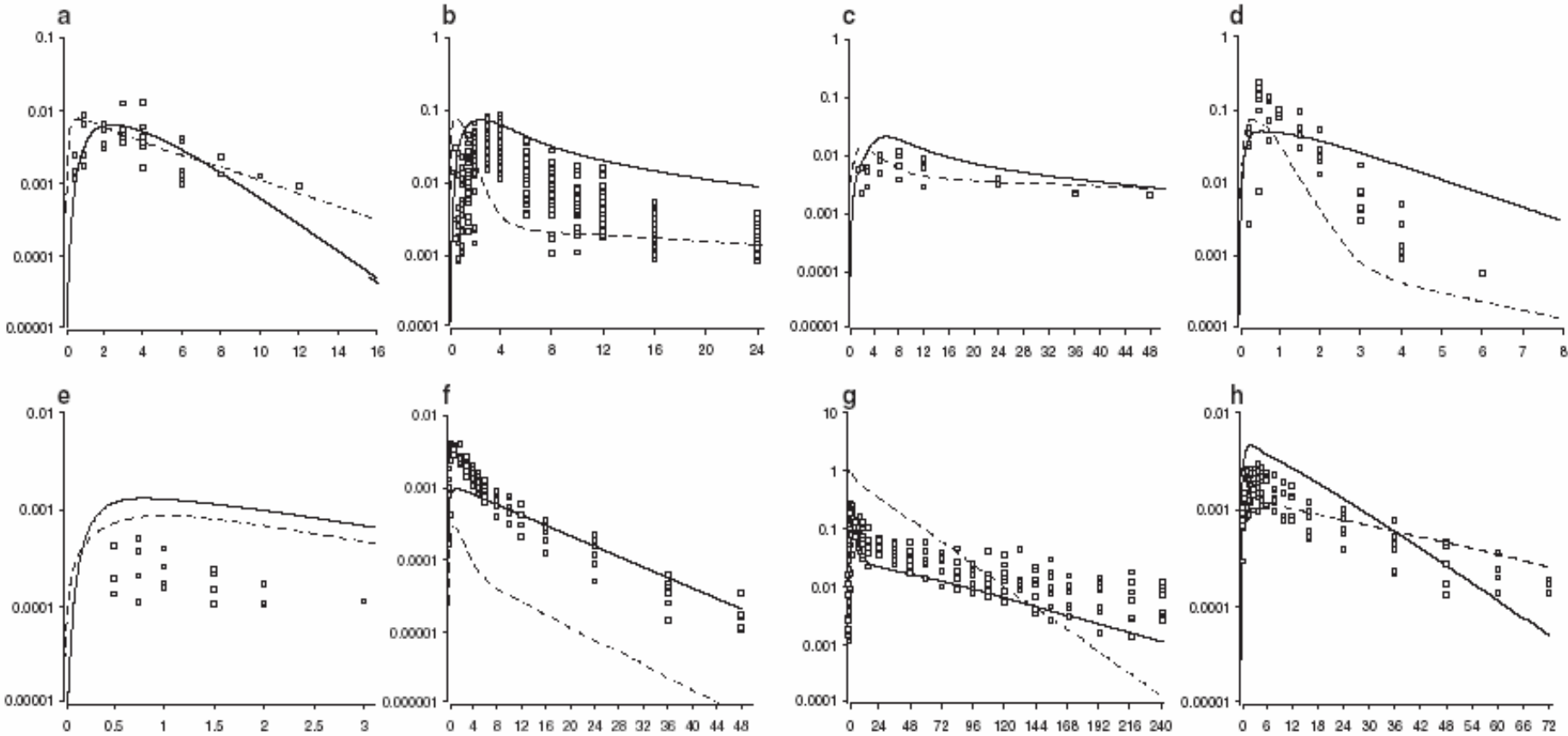


In vivo preclinical data

Any mismatch suggests violation of model assumptions. Additional processes to be considered.



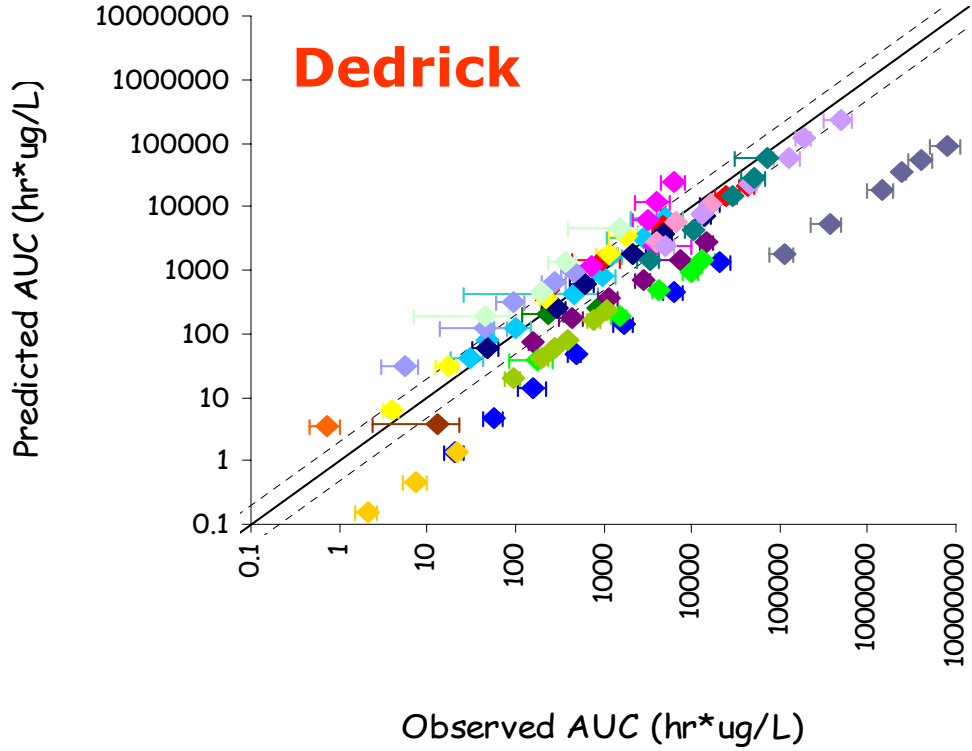
Comparison of PBPK with Allometry



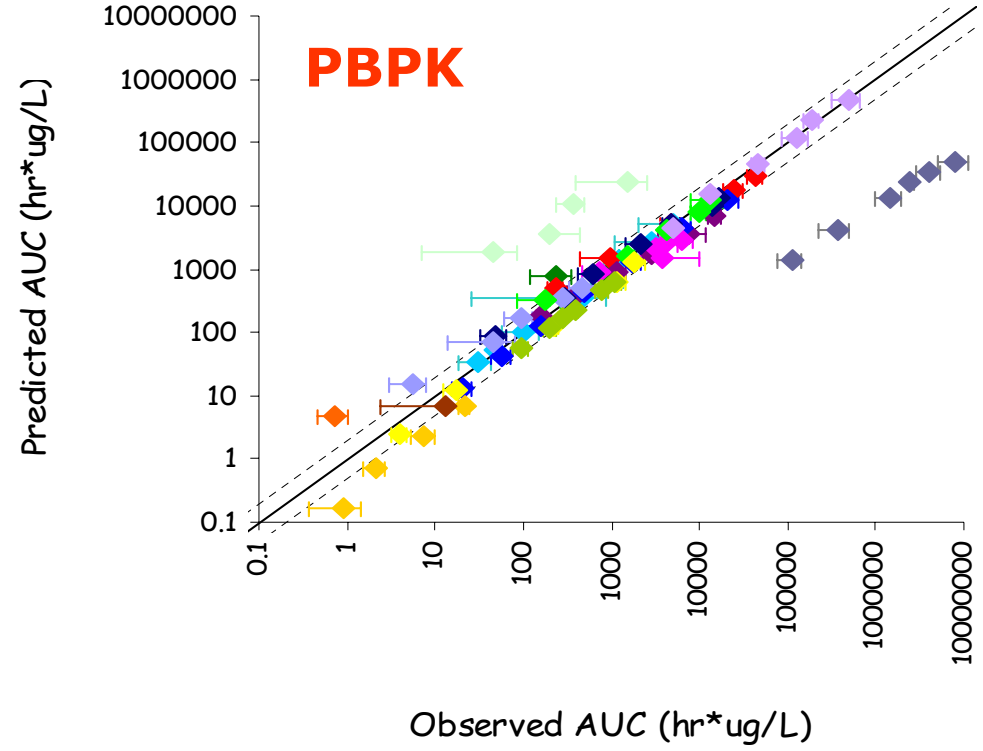
Comparison of PBPK with Allometry



ceuticals



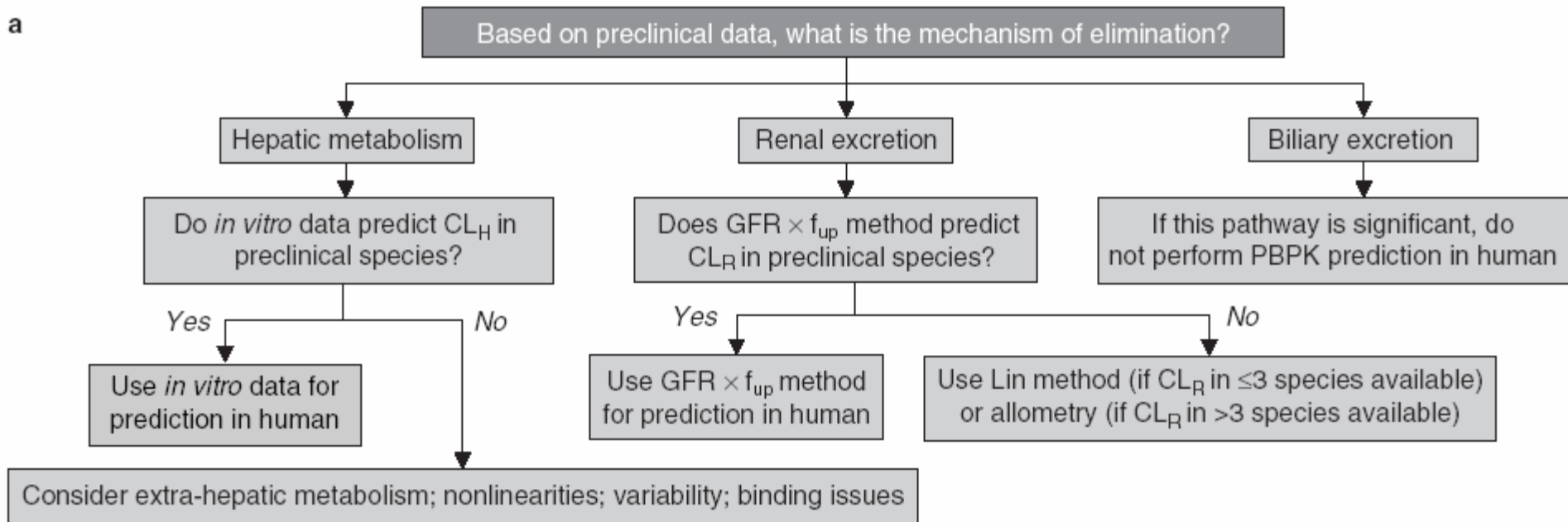
42% of projects within 2-fold error



76% of projects within 2-fold error

Prediction accuracy, PBPK strategy and recognition of uncertainty

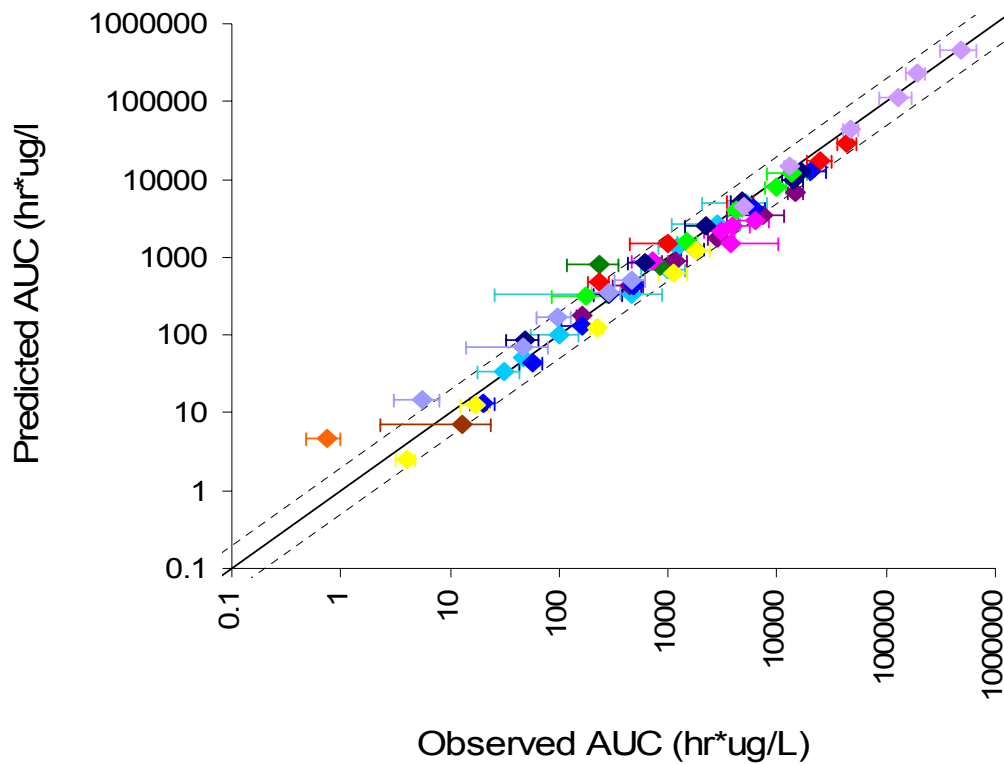
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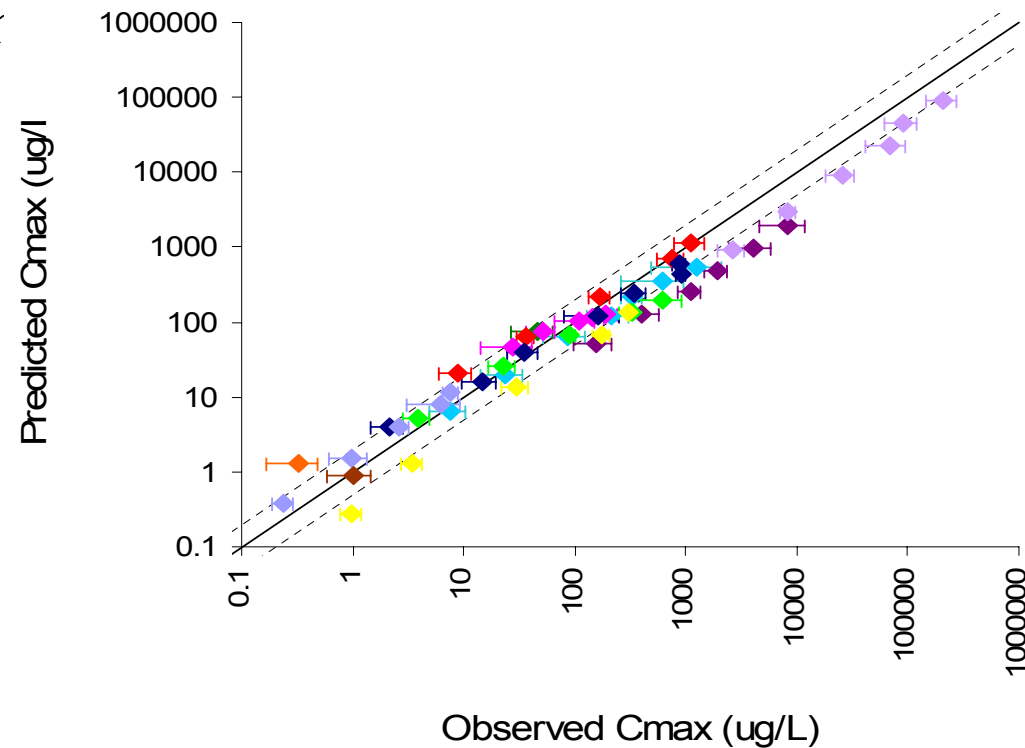
Prediction accuracy, PBPK for compounds with well understood PK processes



rmaceuticals



PREDICTION ACCURACY ~ 90%, n=19



PREDICTION ACCURACY ~ 70%, n=19



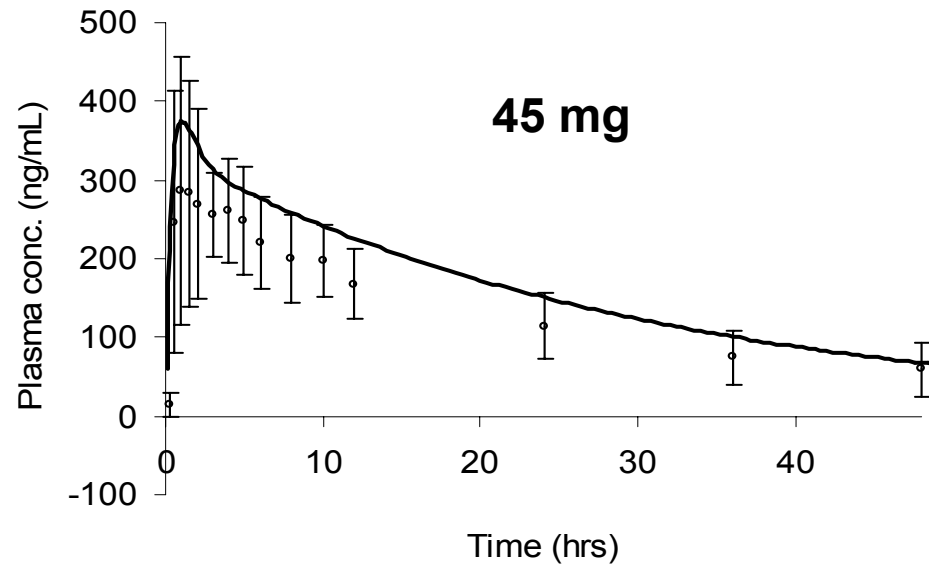
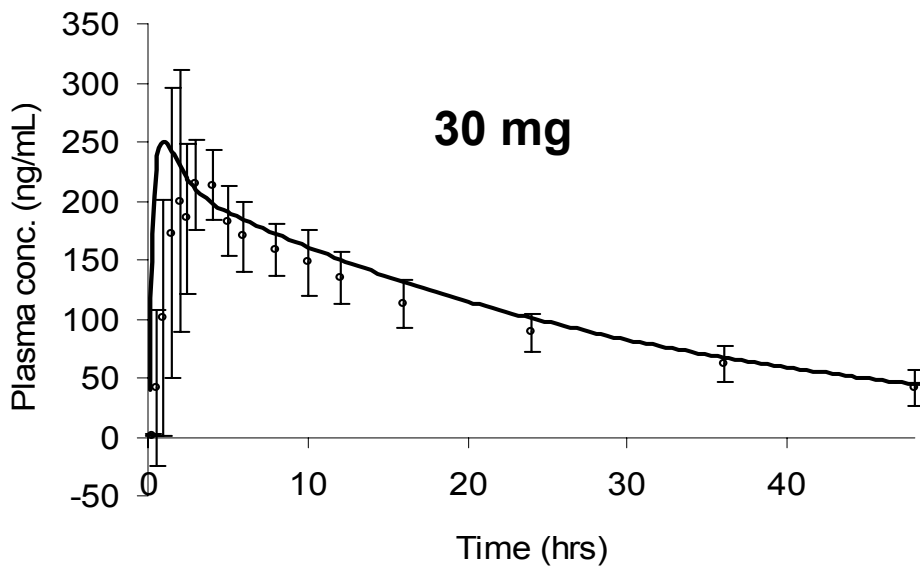
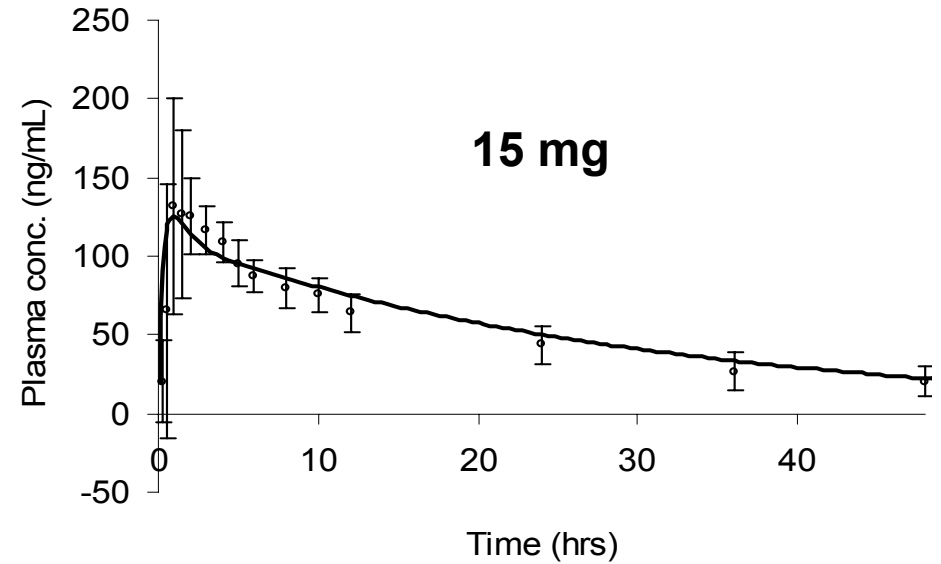
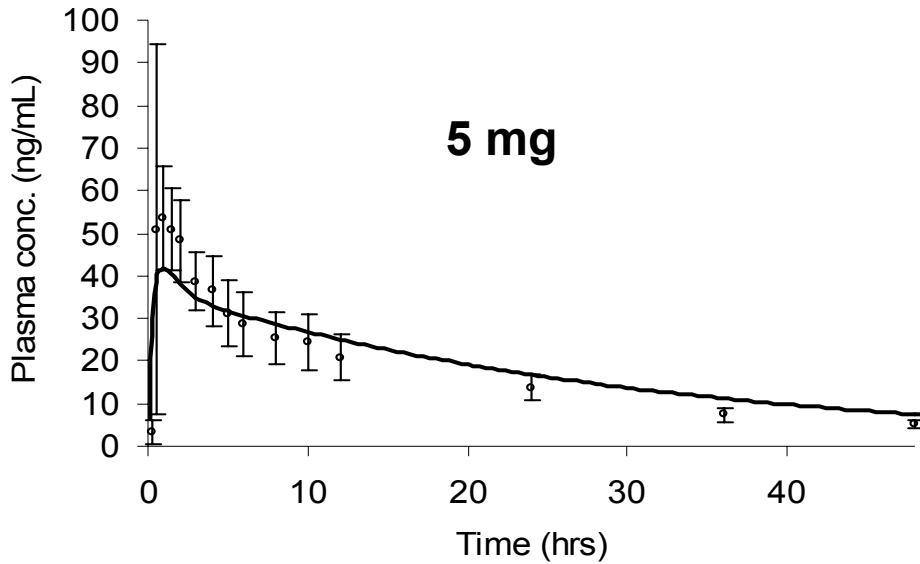
PBPK for prediction in human

- Prediction algorithm proposed where the limits of application have been clearly defined
- PBPK can be applied successfully for ~70% of projects
- Problematic compounds are identified
 - Biliary excretion, enterohepatic recycling, non-linear PK
 - In these cases more caution is needed (e.g. wide range)
- PBPK enables the integration of information, enhancing the understanding of a compound's properties and potentially improving decision making
- Therefore should be applied in this sense to 100% of projects

Prospective prediction for Roche compound X

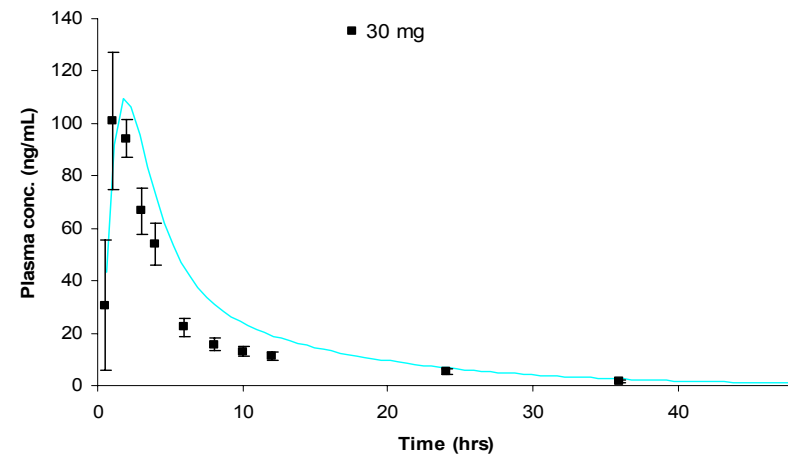
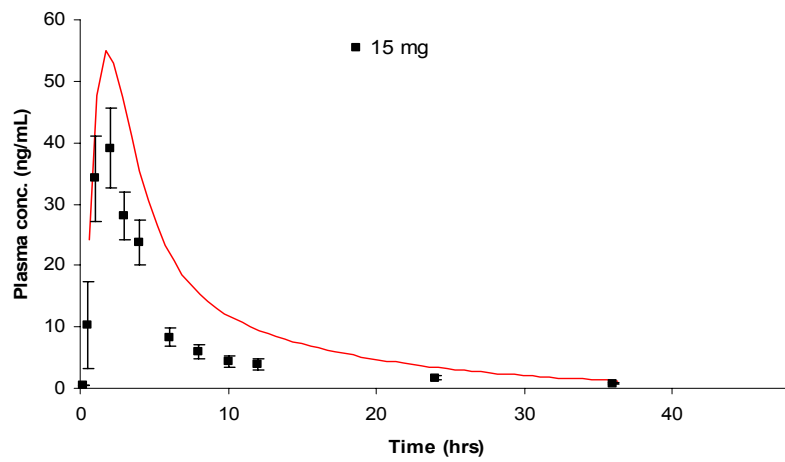
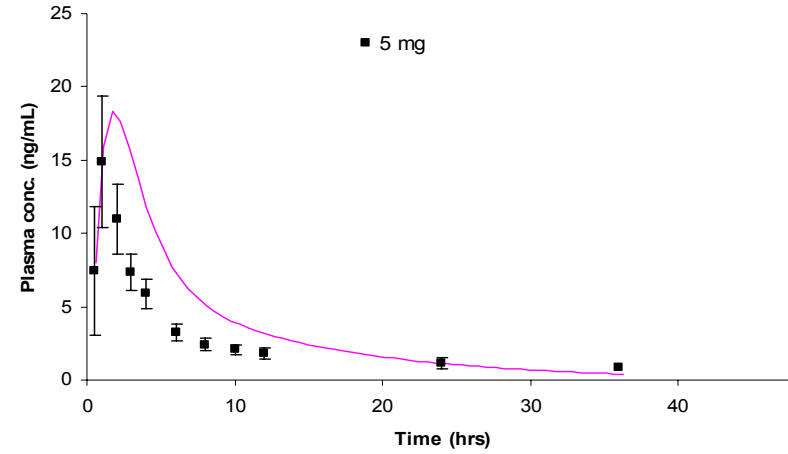
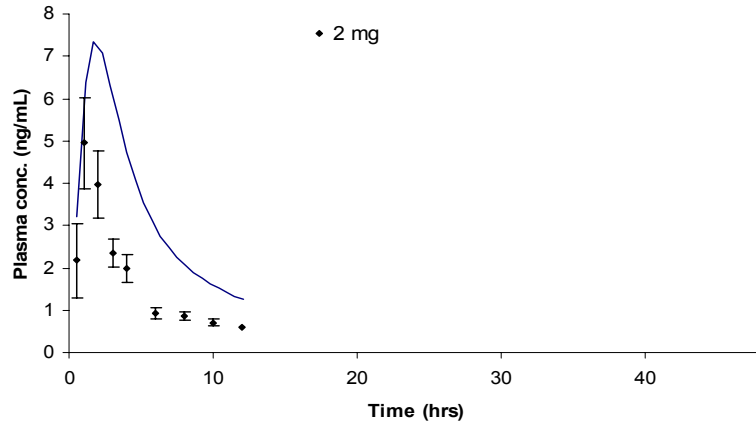


us



Simulated profiles compared to observed conc. (+/-SD)

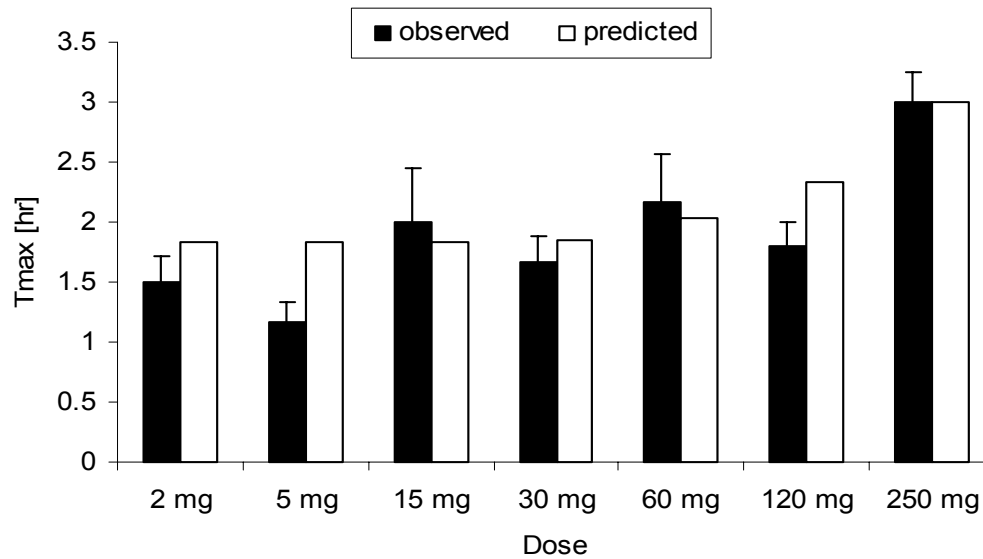
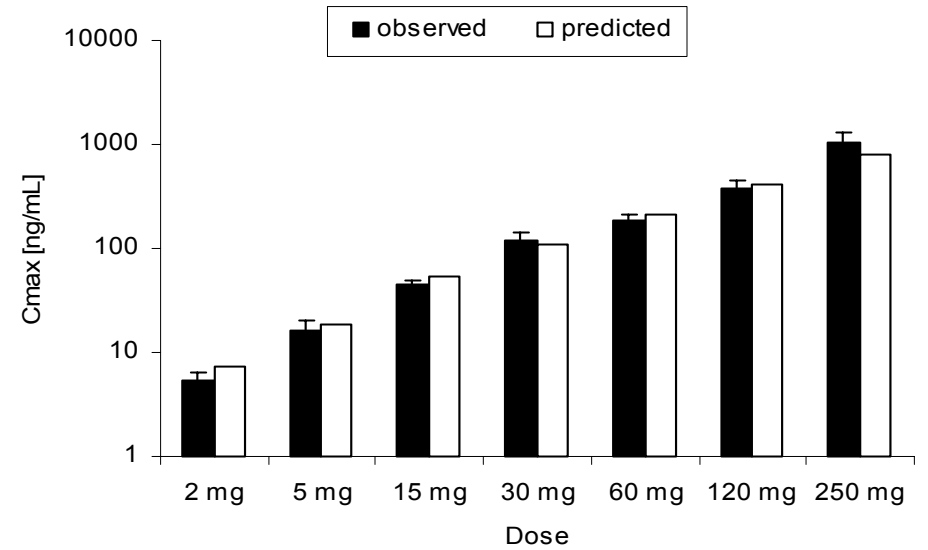
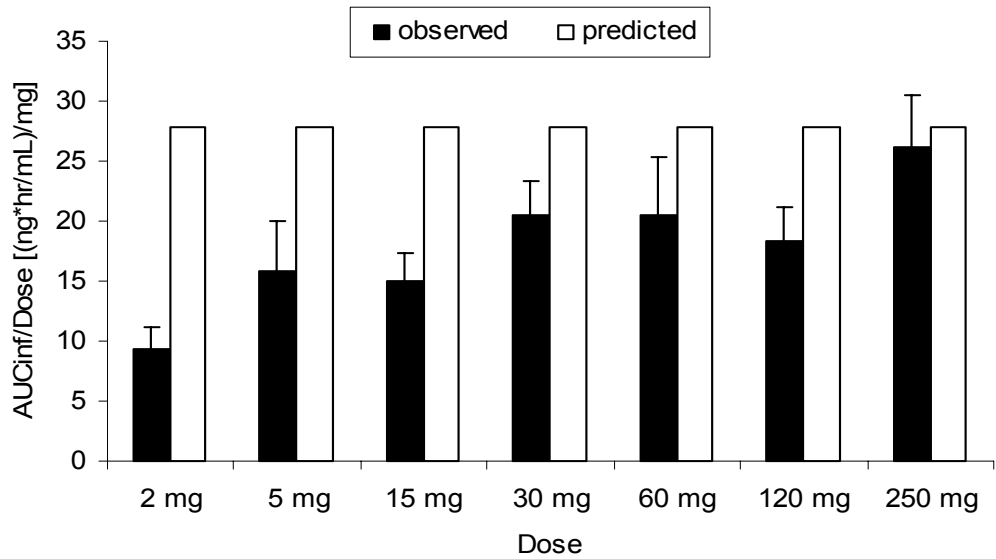
Prospective prediction for Roche compound Y



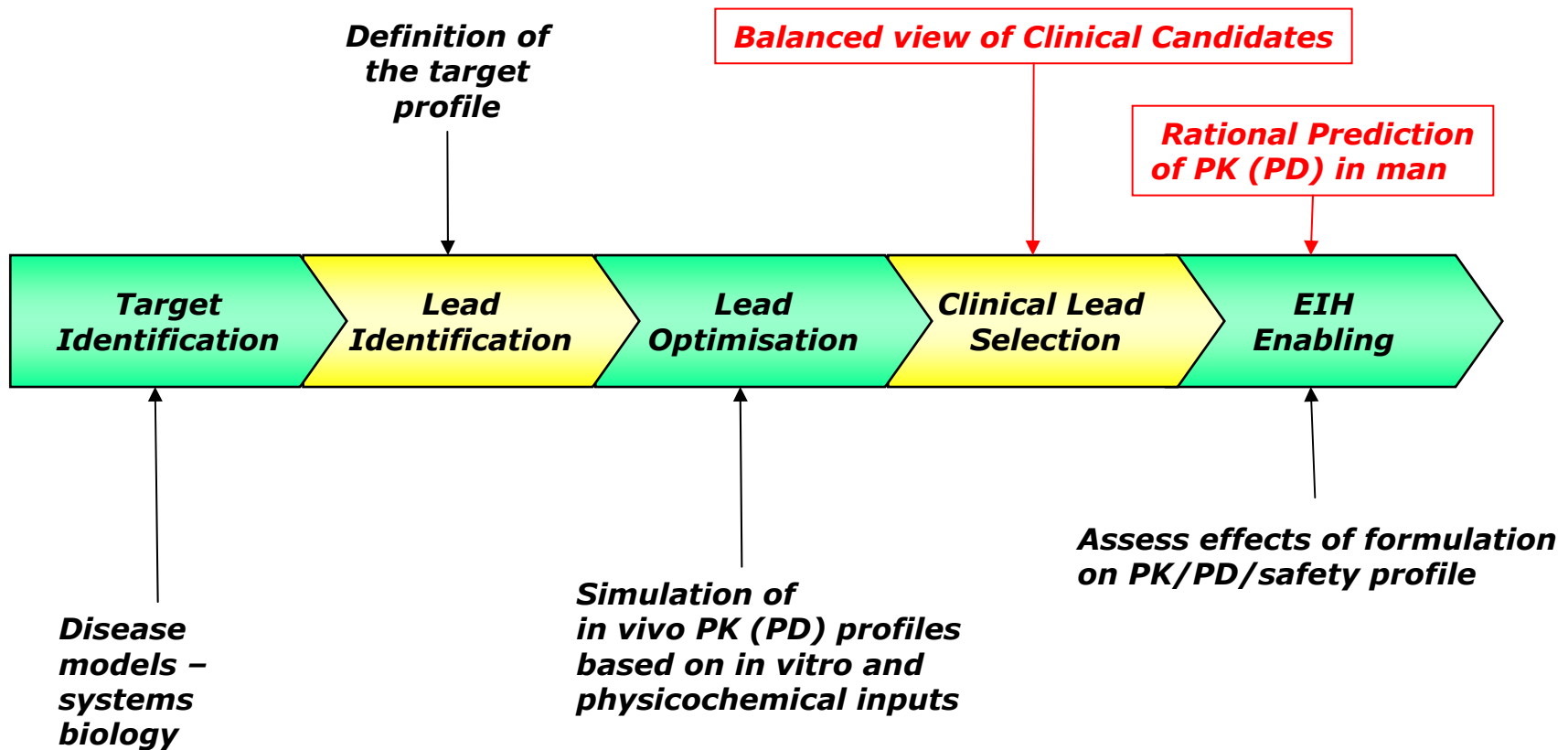
Simulation and observed parameters at different dose levels



icals



Impact of PK prediction during discovery and non-clinical development

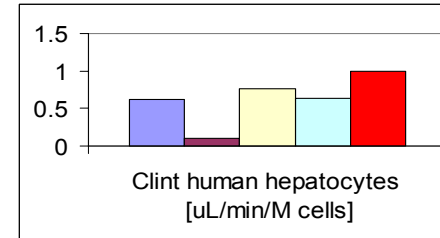
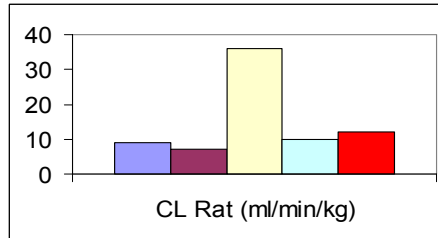




PBPK to aid candidate selection

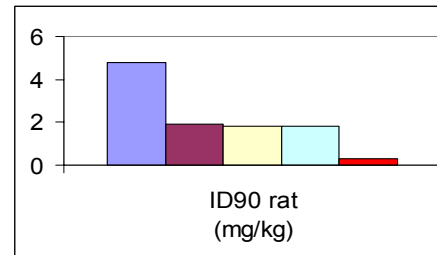
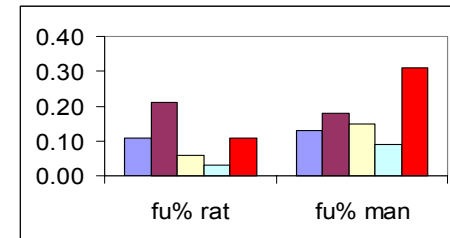
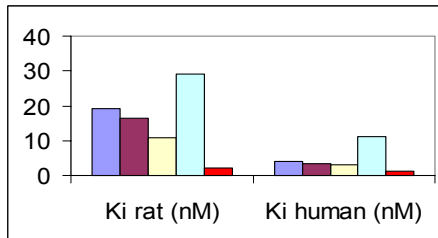
- Aim: to use physiologically based simulation tools to combine the available PK and PD data and assist in selection of the optimal clinical candidate
- Steps taken:
 - Verification: compare simulated and observed PK in rat
 - Predict PK: estimate human PK
 - Predict PD: effective concentrations in human
 - Estimation: Clinical doses and exposures
- Outcome:
 - Balanced comparison of PK/PD incorporating variability and uncertainty to be weighed with other factors (early tox, synthetic tractability, formulation ease etc...)

PBPK to aid candidate selection



Available data for 5 compounds

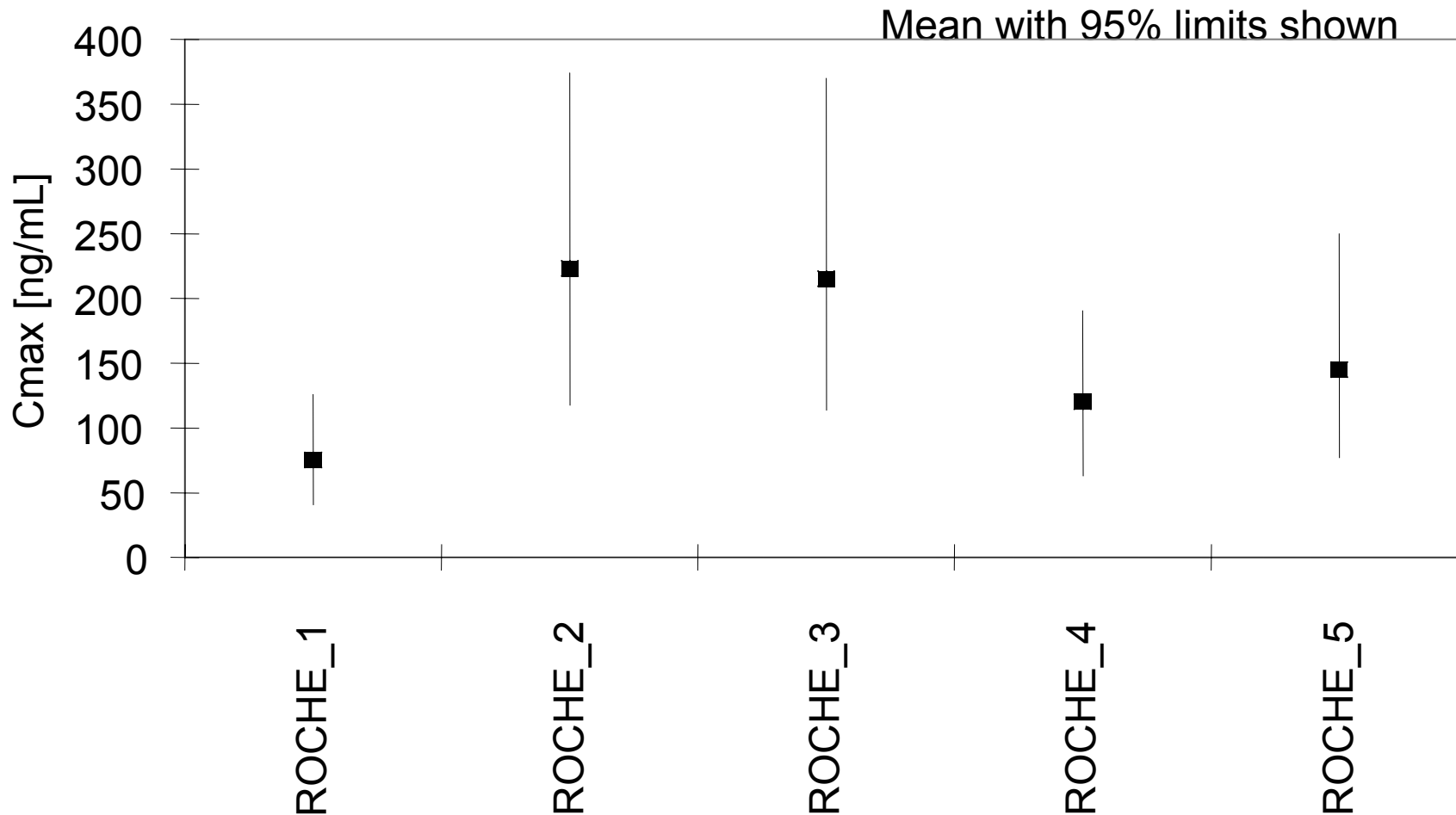
- Physicochemical
- In vitro hepatocytes rat & man
- Protein binding rat & man
- In vivo PK i.v. and p.o. in rat
- Effect versus concentration in rat



PBPK to aid candidate selection



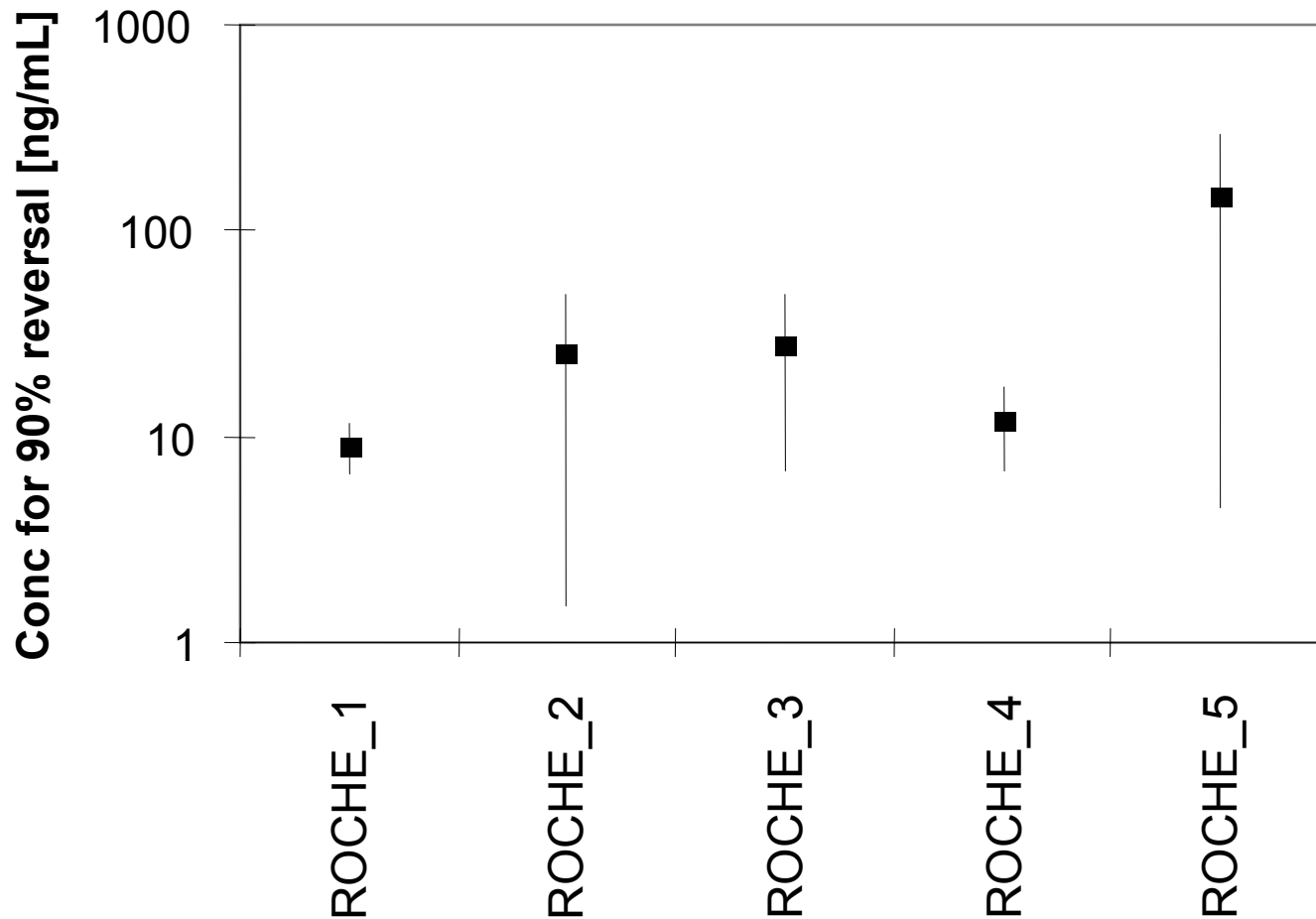
Simulated **C_{max}** in Human for a dose of 25mg including variability in both CL and V based upon in vitro and in vivo data



PBPK to aid candidate selection

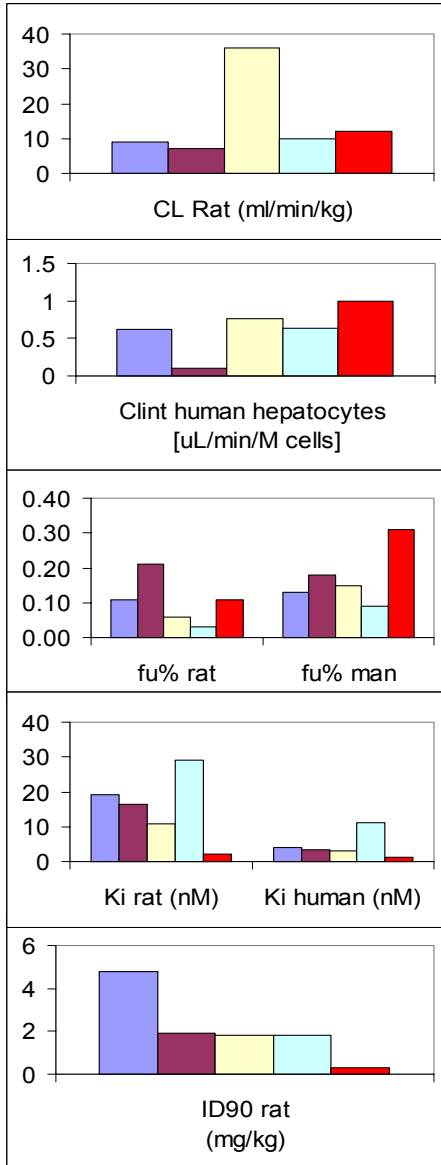


Effective concentration in Human estimated from rat PD data rat and in vitro data in both species (Fu% rat & human, Ki rat & human)

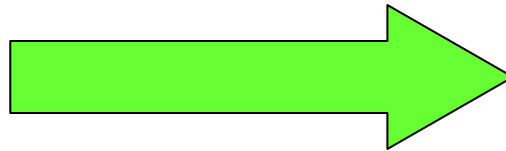


Variability is based on the observed variability in the rat

Multiple Discovery Data



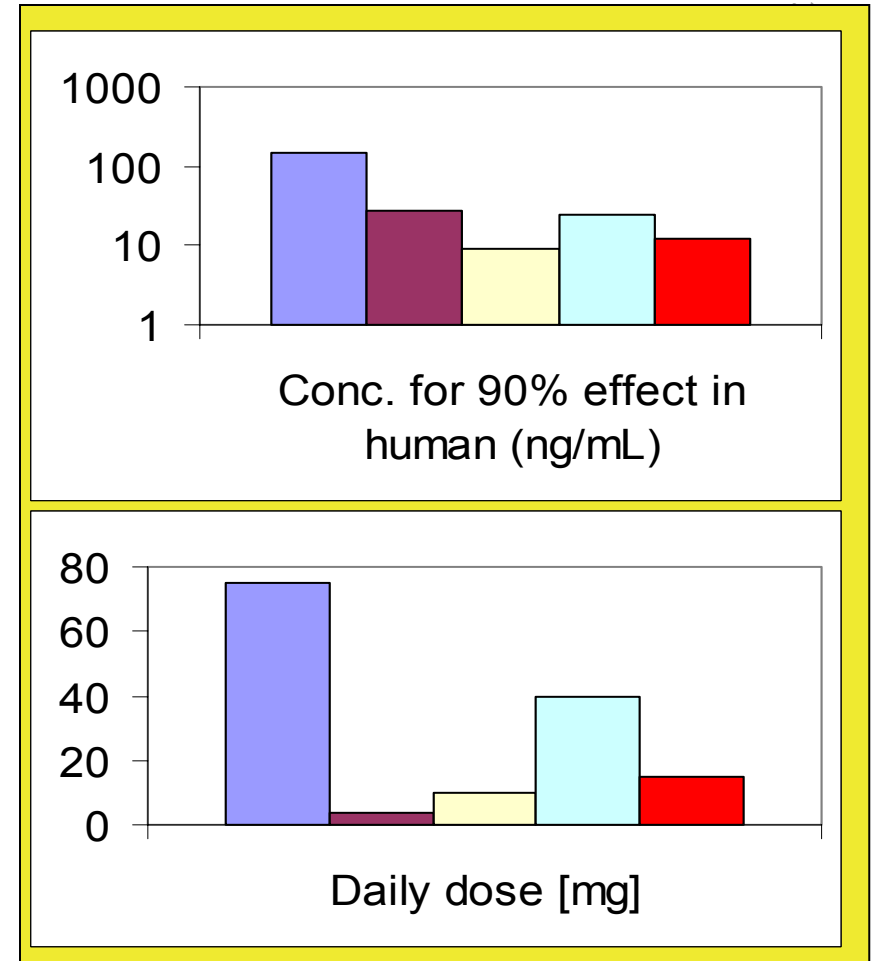
Simulation



- Integrates multiple PK and PD data
- Aids rational and balanced decision
- Focuses on expected human PK/PD

Prediction in Human

euticals



Neil Parrott, Hannah Jones, Nicolas Paquereau and Thierry Lave
 Basic & Clinical Pharmacology & Toxicology 2005, 96, 193-199.

PBPK, gaps

- Lacking mechanistic models and predictive in vitro data for
 - Biliary elimination, renal elimination, extra-hepatic metabolism, transporters in general
 - Formal strategy for inclusion of variability
- Is PBPK applicable during lead optimisation?
 - Input data is more uncertain and incomplete
 - In silico predictions?
 - Need in vivo data to verify models for compound classes
 - The tools and techniques are too complex and time consuming
 - Rapidly becoming no longer valid given good data management and recent developments in user friendly software



PBPK in Pre-Clinical Research

Conclusions

- Physiologically based PK models are useful to drug discovery for
 - candidate selection
 - human PK prediction
- Generic models should be applied early and then refined and improved - models develop as a compound progresses and more data become available
- There is scope for wider use and maximal value will be realized when PBPK simulation is adopted by non-modelers currently using only more traditional approaches

Acknowledgements



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Sandwich

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