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# Introduction to PBPK

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# Outline


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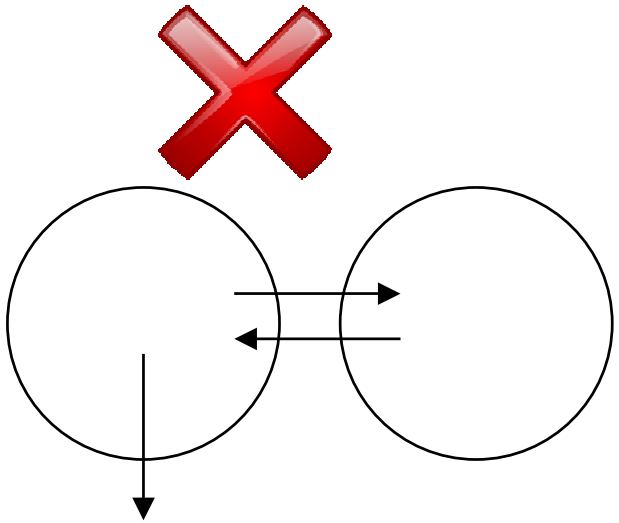
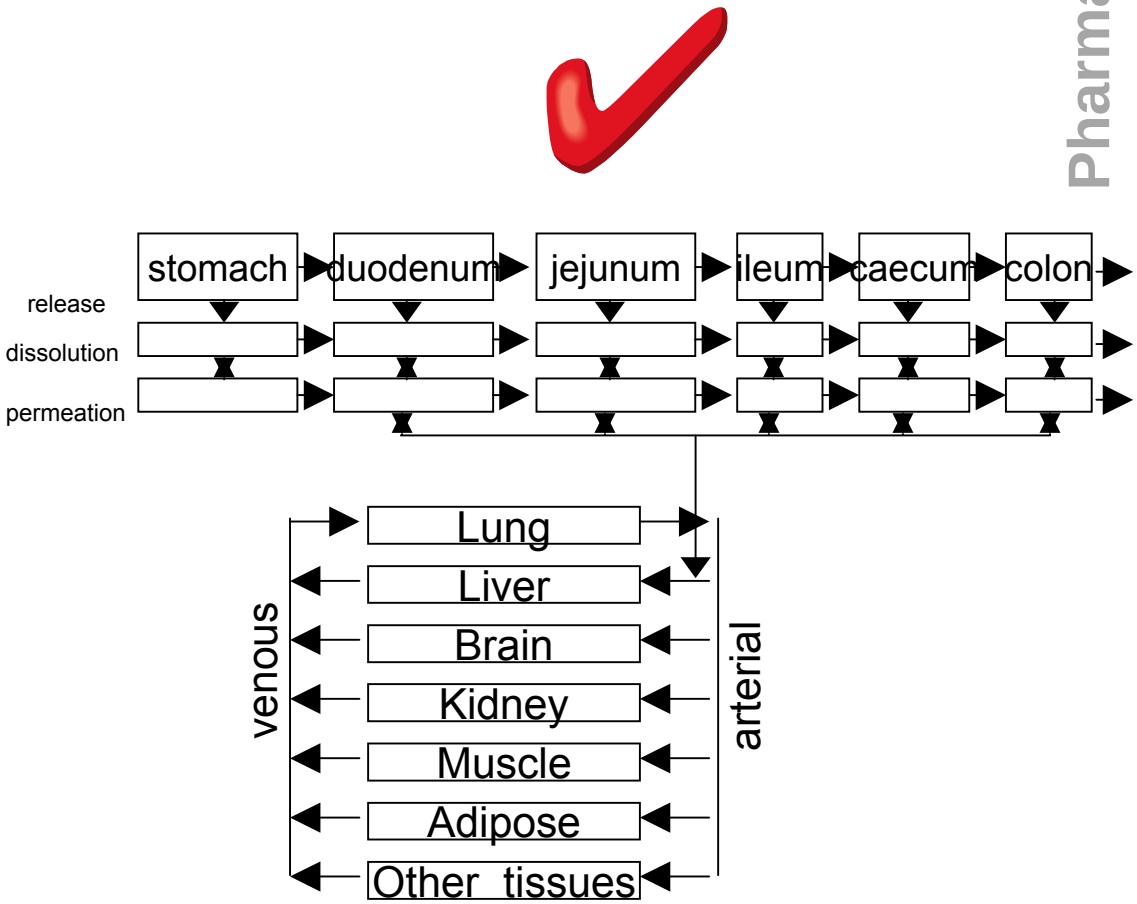
- Introduction
  - What is PBPK?
  - PBPK models of absorption, distribution and metabolism and elimination
- Application of PBPK in pharmaceutical research and development
  - Past uses
  - Recent developments
- Experience at Roche
  - Extrapolation of human pharmacokinetics
  - Some benefits of the PBPK approach from discovery to the clinic
- Considerations for PBPK modeling in pediatric populations

# What is physiologically based pharmacokinetic (PBPK) modeling?

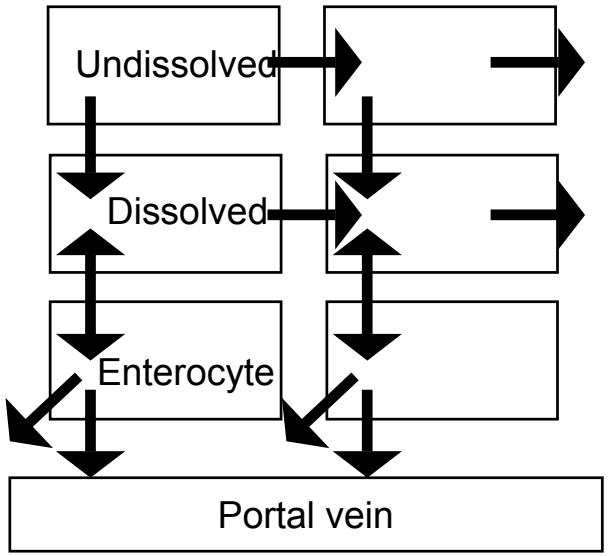
$$C(t) = \sum_i C_i \, e^{-k_i t}$$






Aarons, L., British Journal of Clinical Pharmacology, 2005. **60**(6): p. 581-583.

# Absorption

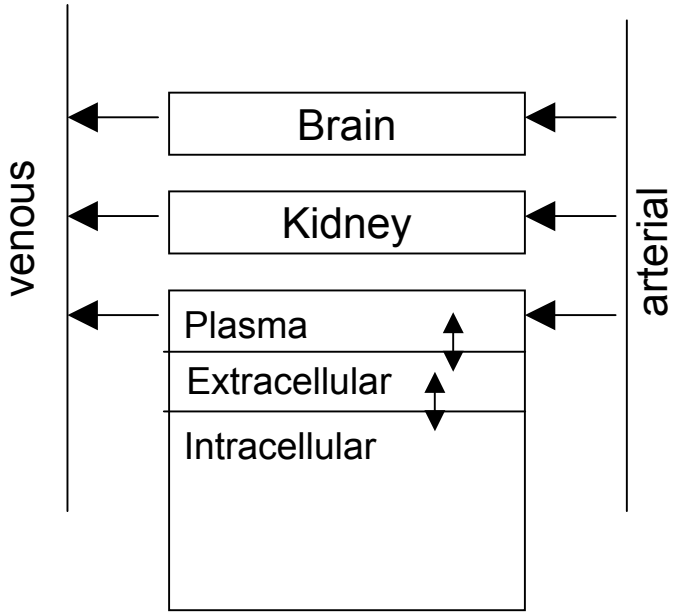



Model parameters include :

| Physiology | Drug specific |
|---|---|
| Intestinal fluid volume | Solubility |
| Intestinal transit times | Particle size |
| Intestinal pH | Charge |
| | Lipophilicity |
| Luminal surface area | |
| Metabolizing enzyme expression | Formulation |

Agoram, B., W.S. Woltosz, and M.B. Bolger,. Adv. Drug Deliv. Rev., 2001. **50**(Supplement 1): p. S41–S67.

# Distribution

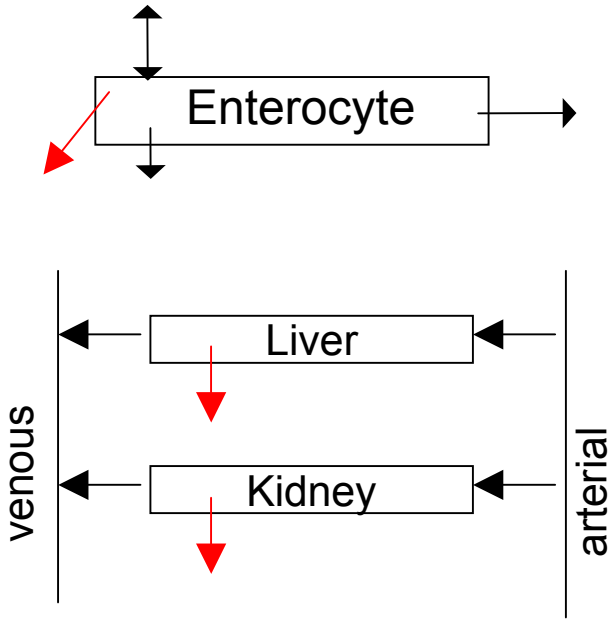



Model parameters include :

| Physiology | Drug specific |
|---|---|
| Blood flow | Lipophilicity |
| Tissue perfusion | Charge |
| Tissue volume | Tissue partitioning |
| Tissue composition | Plasma protein binding |
| | Membrane permeability |

Rodgers, T. and M. Rowland,. Pharmaceutical Research, 2007. **24**(5).

# Metabolism/Elimination




Model parameters include :

| Physiology | Drug specific |
|---|---|
| Blood flow | Drug lipophilicity |
| Enzyme amounts | Drug charge |
| | Plasma protein binding |
| | Membrane permeability |
| | Enzyme kinetics |

Rostami-Hodjegan, A. and G.T. Tucker, Nat Rev Drug Discov. 2007. 6(2): p. 140-148.

# Some key benefits of PBPK

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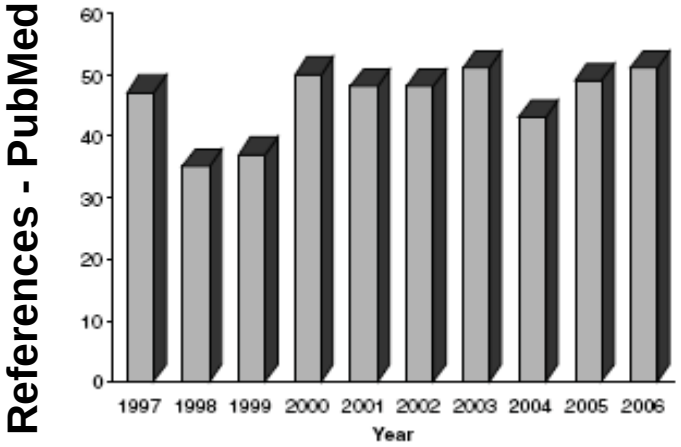
- Framework for integration of *in-vitro* data
- *a priori* prediction of PK is feasible
- Kinetics in tissue (effect) compartments can be estimated
- Extrapolation across species, routes of administration and doses
- Modeling of sub-populations (e.g. obese patients,  elderly)
- Modeling of variability and uncertainty

**BUT**

- Although the benefits are numerous the growth in use has been at best steady




Nestorov, I., Expert Opin. Drug Metab. Toxicol., 2007. **3**(2): p. 235-249.

# PBPK : Time for wider use?

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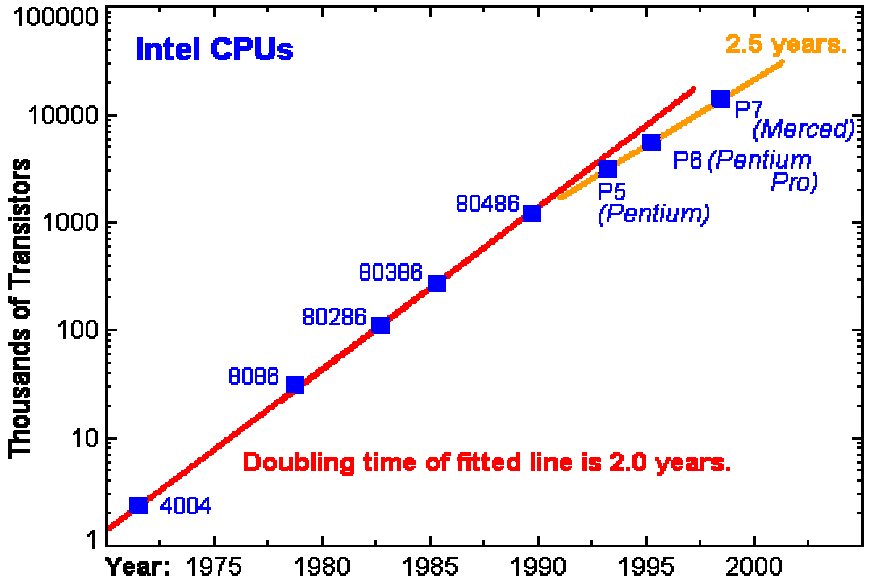
- Limitations in computing power – but this is not a factor for some years
- PBPK too complicated ?
- Shortage of experts ?




- Tools are now very user friendly
- Training and support available

SIMCYP real solutions from virtual populations

PK-Sim®

GastroPlus™

# PBPK for extrapolation of human PK

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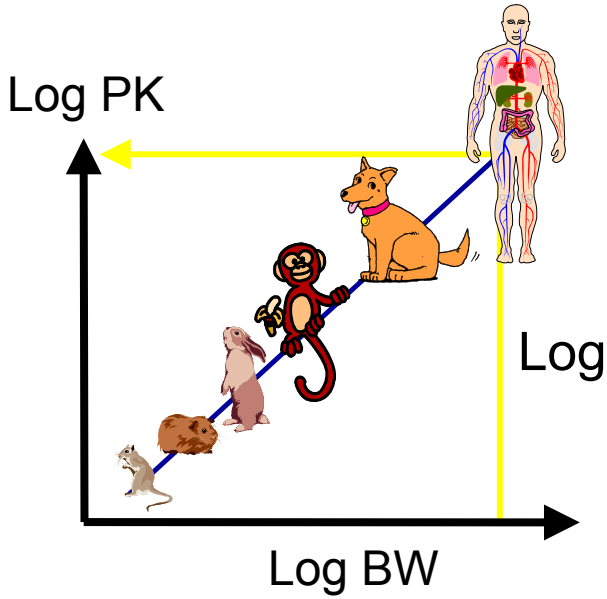
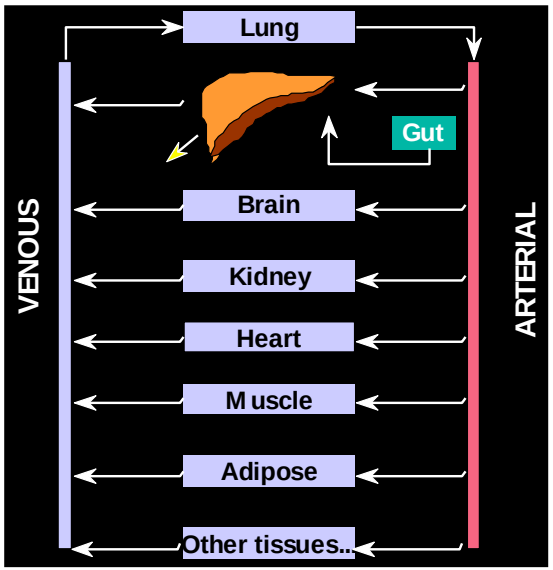
## Empirical Methods




$$\text{Log PK} = a \bullet BW^{y}$$

+ 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
+ easily inked to PD models
+ potential to predict metabolites

# A strategy for human PBPK predictions

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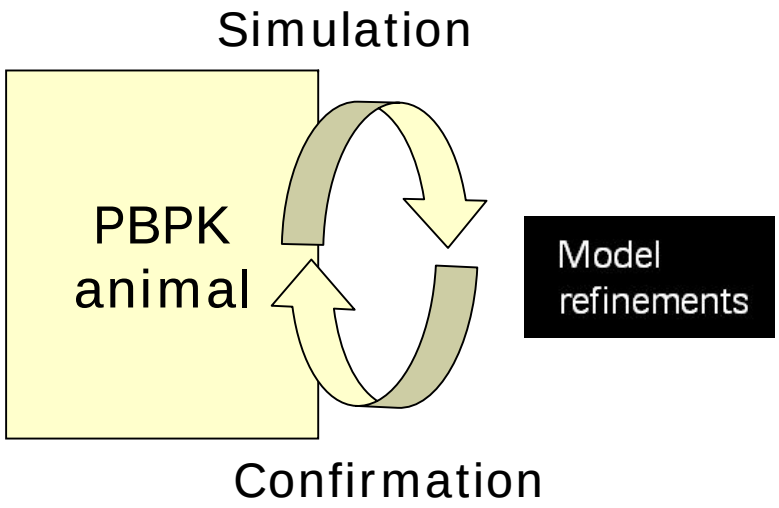
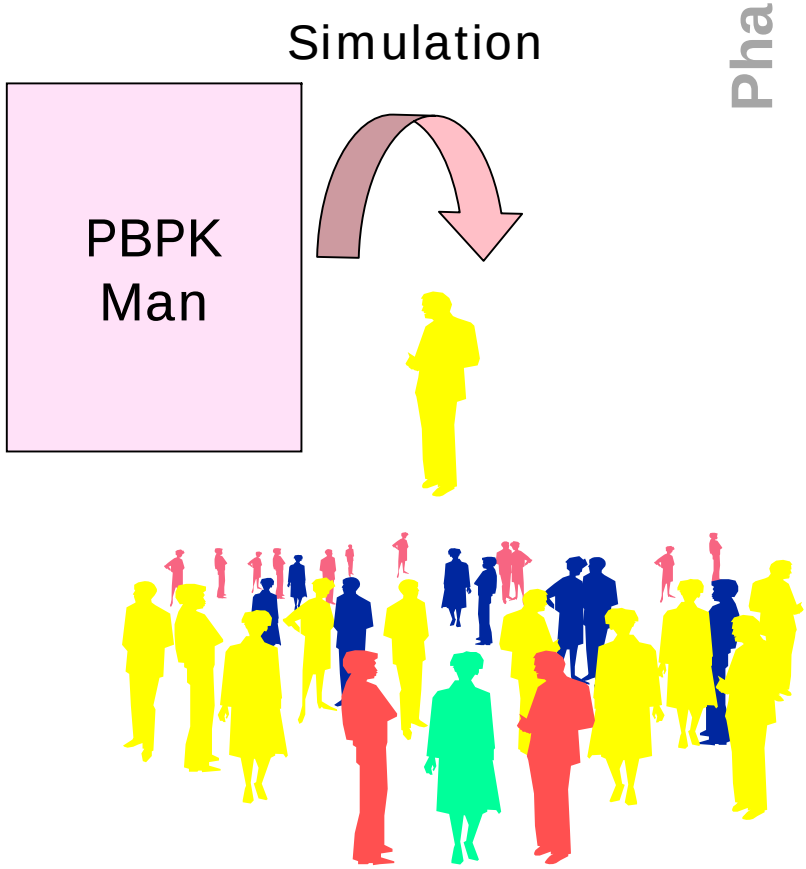
Molecular descriptors; in vitro and in silico ADME data




In vivo preclinical data

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

Jones, H., et al., Clinical Pharmacokinetics, 2006. **45**(5): p. 511-542.

# PBPK model refinements

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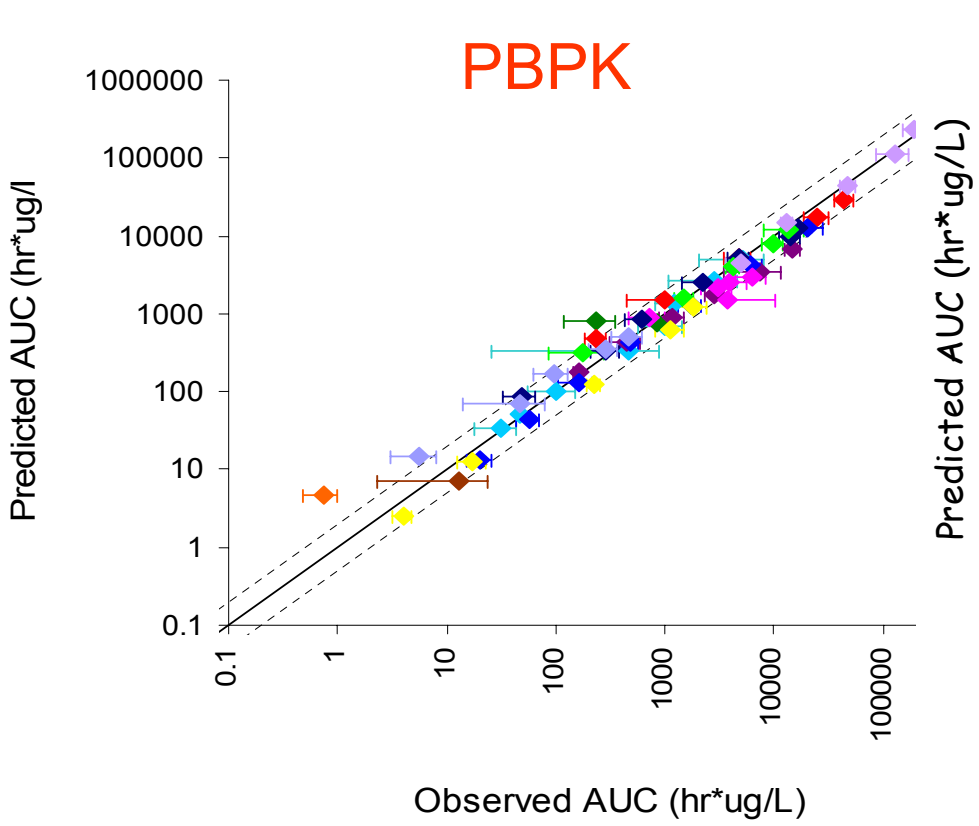
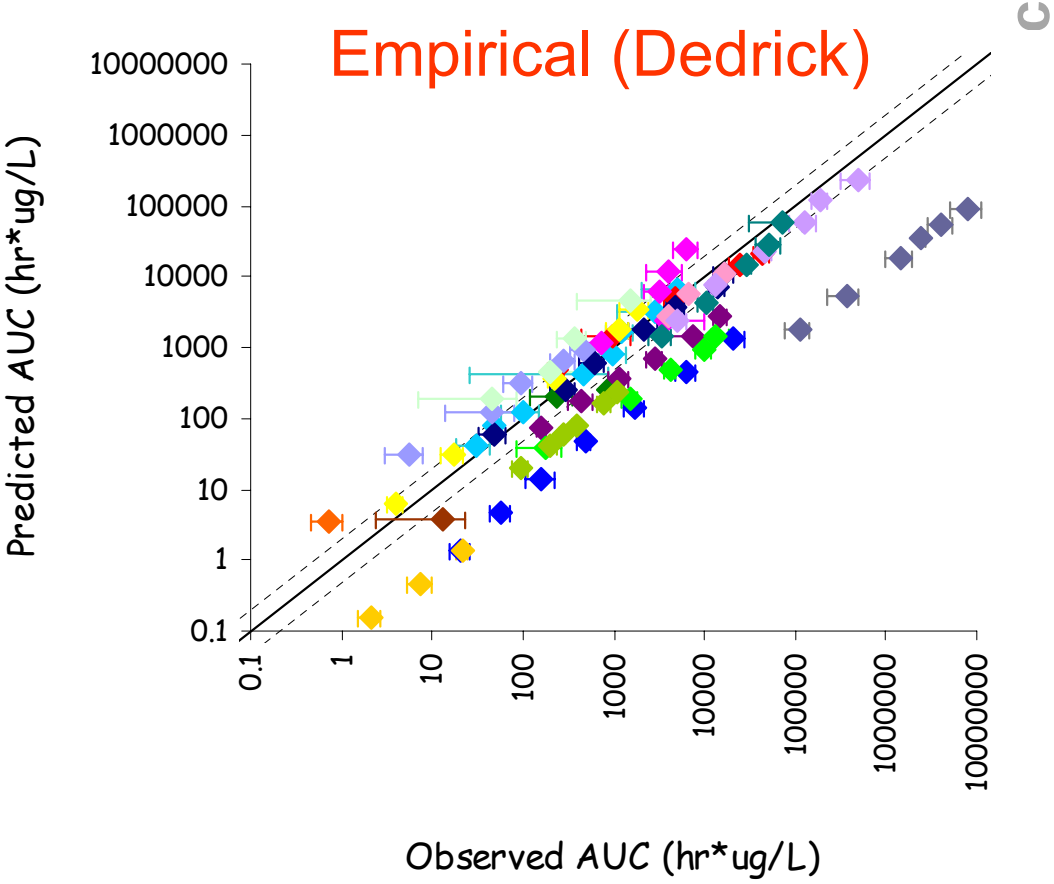
| | Absorption | Clearance | Distribution |
|---|---|---|---|
| **Preliminary** | Aqueous solubility<br>PAMPA or in silico permeability | Liver microsomes<br>Predicted binding<br>Well stirred model | Predicted tissue partitioning<br>Perfusion limited |
| **Refined** | Biorelevant solubility<br>Caco2 permeability<br>Intestinal metabolism<br>Efflux / Influx transport<br>GI fluid degradation<br>Formulation effects | Hepatocytes<br>Active transport processes<br>Measured in vitro binding Renal clearance<br>Biliary excretion | Measured tissue partitioning (rat)<br>Permeability limited tissue model with active transport |

# PBPK accuracy superior to empirical methods




**PREDICTION ACCURACY ~ 90%, n=19**




**PREDICTION ACCURACY ~ 40%, n=19**

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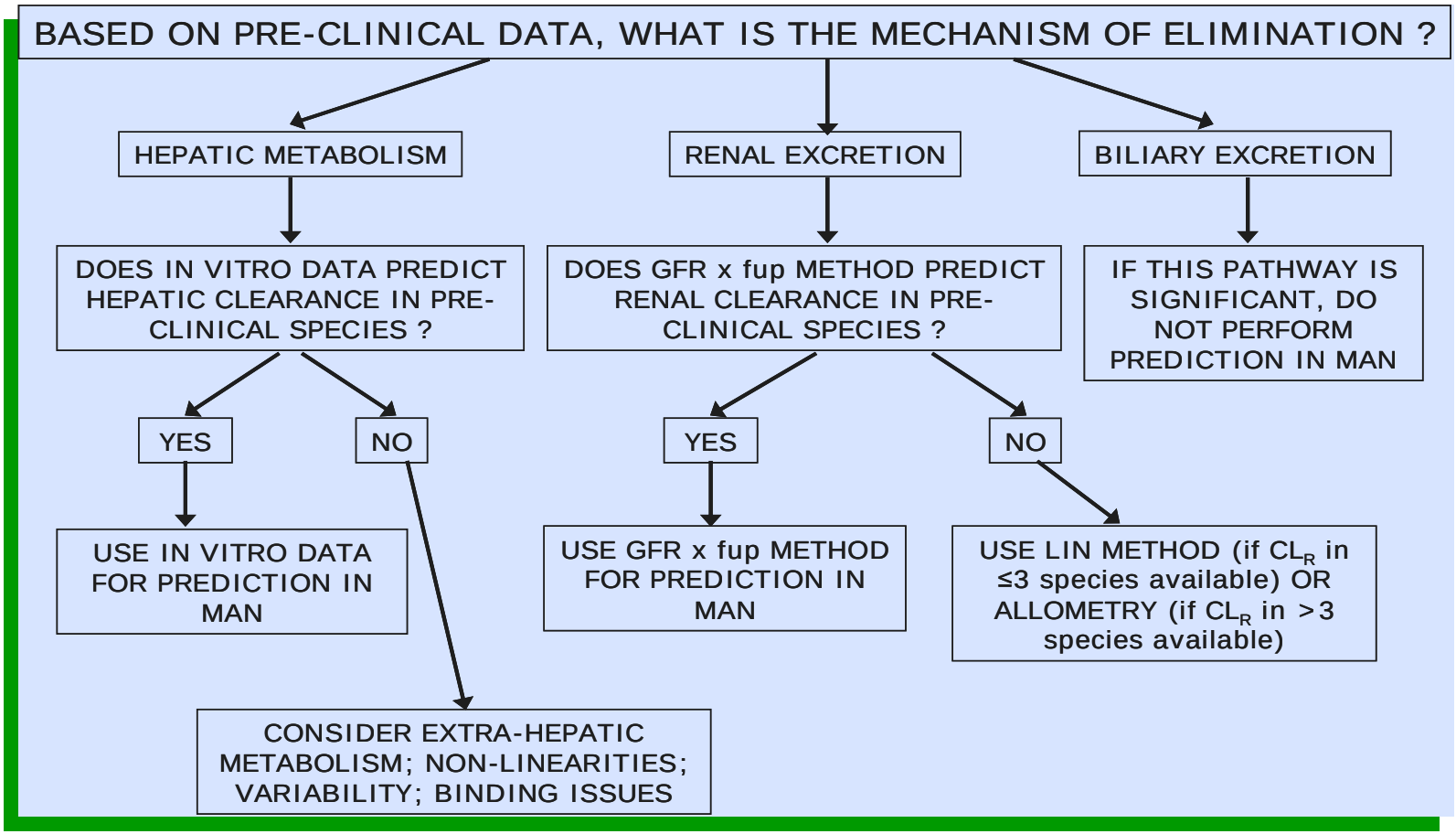
# PBPK additional benefits in understanding

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# PBPK throughout research and development

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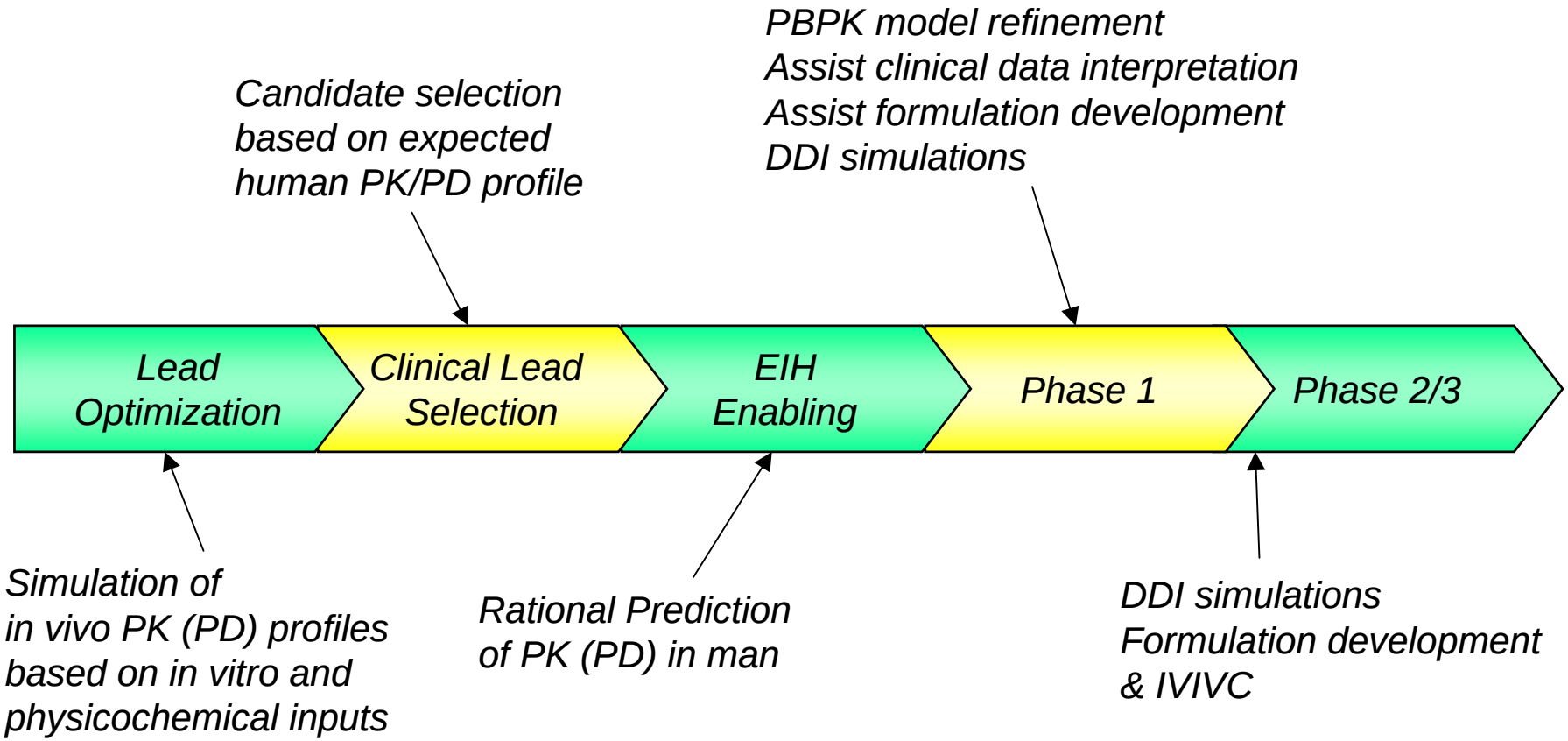

# Considerations for a PBPK model in pediatrics

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- Existing PBPK in adults can be leveraged
- PBPK allows the known physiological differences between adults and children to be accounted for
  - E.g. changes in body fat, plasma proteins, organ size development,
- Known maturation in clearance processes can be incorporated
  - E.g. specific cytochrome P450s and renal clearance maturation
- Allows variability to be included (e.g. in clearance as shown by Johnson)
- Several examples of application are encouraging as to the benefits of this approach


Bjorkman, S.,. British Journal of Clinical Pharmacology, 2005. **59**(6): p. 691-704

Johnson, T. et al.. Clin Pharmacokinet, 2006. **45**: p. 931-956.

Edginton, A.N., et al. Clinical Pharmacokinetics, 2006. **45**(10): p. 1013-1034.

# Acknowledgements


- T. Lave
- B. Reigner
- H. Jones


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