Addressing Drug Development Questions With Physiologically-Based Pharmacokinetics (PBPK)

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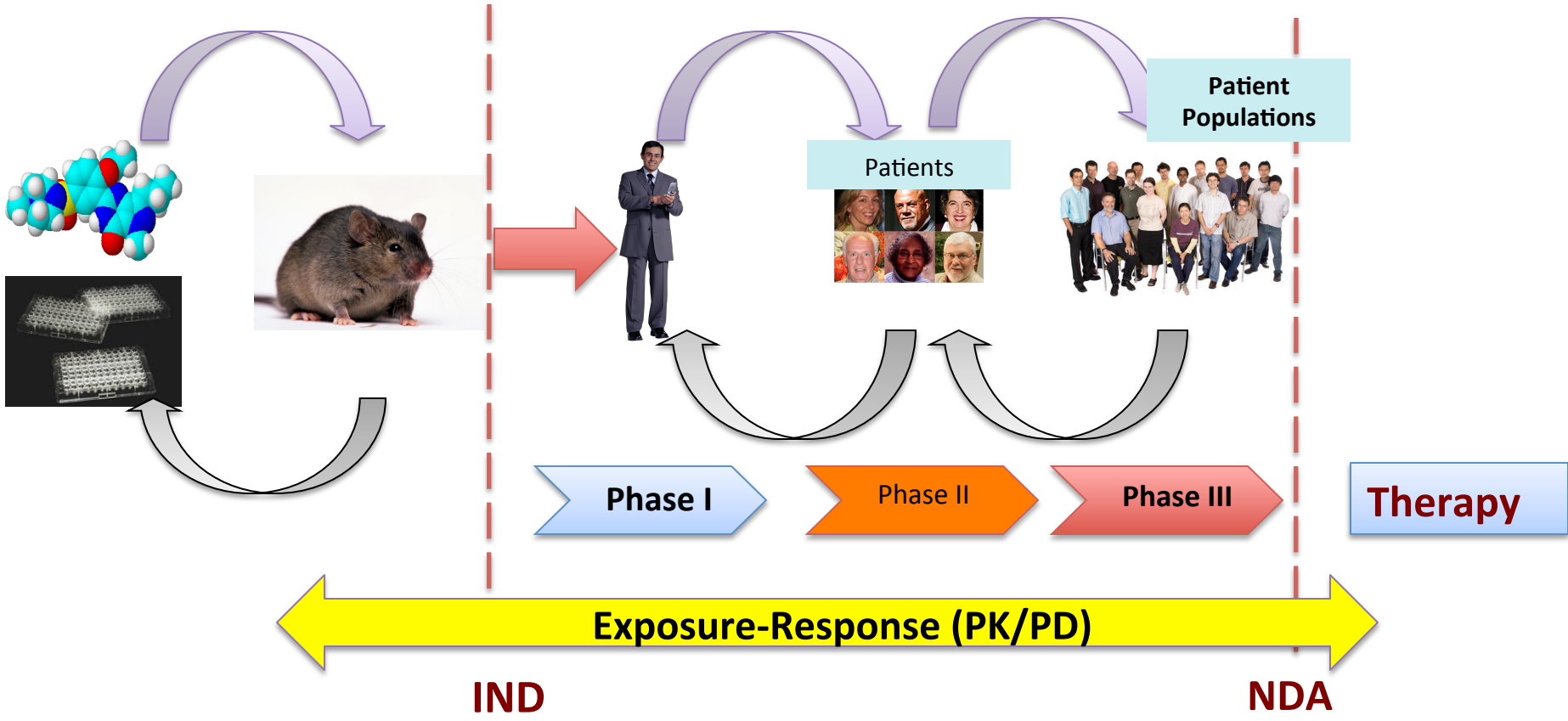
Outline

- Why is PBPK need
- The model structure
- Why now, not before
- Prediction of initial human PK
- Application to clinical development
- Concluding remarks
- Application to small molecules
- Broad overview

Reading material

- Rowland, Peck, Tucker. Physiologically based pharmacokinetics: Applications to Drug Development and Regulatory Sciences. *Ann. Rev. Pharmacol. Toxicol*. **51**, 45-73, 2011

Stages in Drug Development

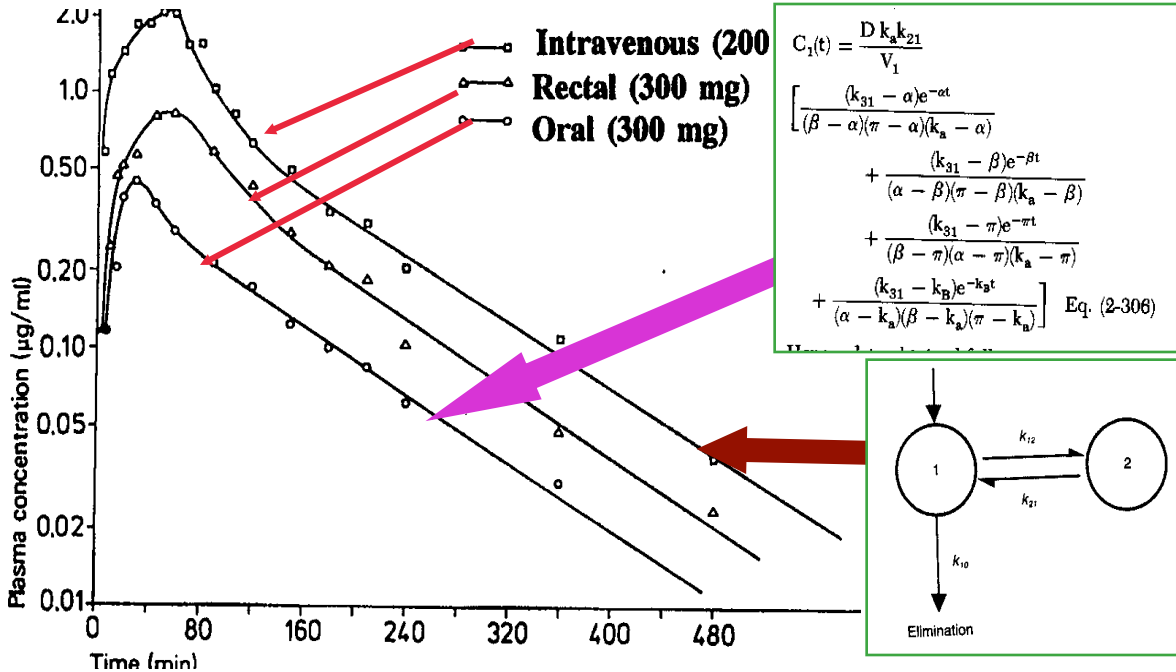


PK questions that we would like to have answered.

- Can we reliably predict quantitatively events in humans from in vitro, animal and other information? FIH
- Can we explain differences across compounds? Candidate selection.
- Can we predict likely variability in target patient population under clinically realistic conditions. Clinical development, and therapeutic use.
- Why do we get the profiles we see?

Standard Approaches to defining PK

- **An empirical equation**
- **Compartmental model**

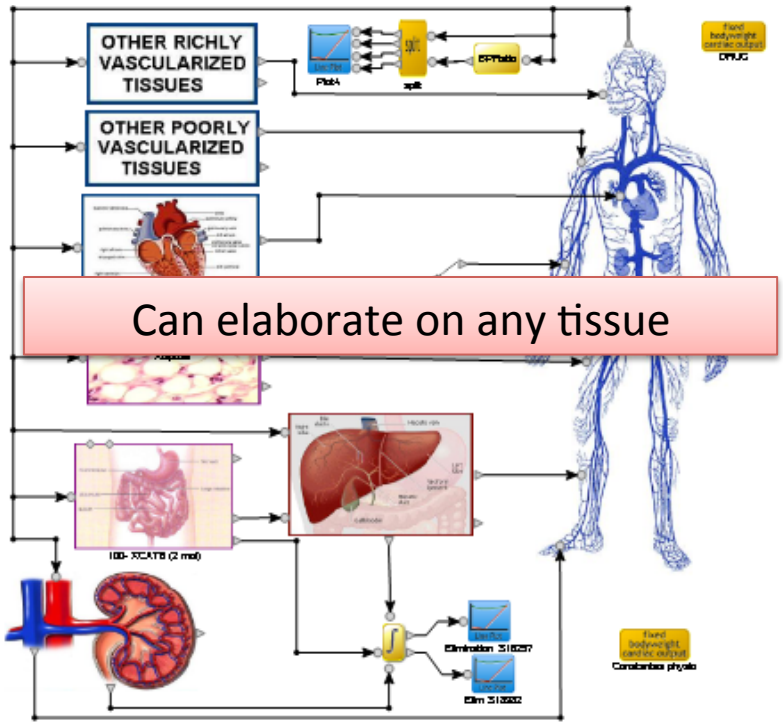


Both approaches deal essentially only with the observations. That is, choose an equation or compartmental model that best describes the data.

Limited mechanistic understanding and predictability, and poor in addressing the previous questions.

Solution: Physiologically based PK (PBPK)

- **Physiological Parameters**
  - Blood flow, tissue size , composition, etc
  - Enzyme, transporter activity
  - Genetics, disease, age, sex, etc
  - Independent of drug (system properties)
- **Compound Specific Parameters (overlaid onto system)**
  - Clearance, tissue affinity.
  - Membrane permeability, transport
  - Inhibitory and inducer potential…
- **The model structure: common to all mammals**. Complexity may vary



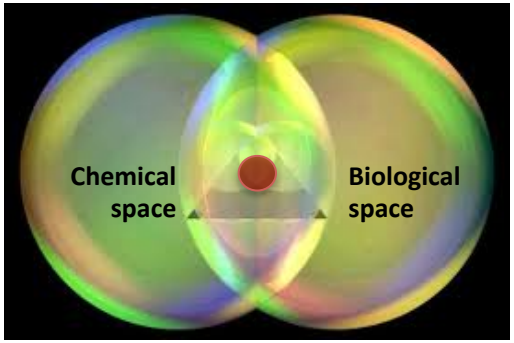
Francois Bouzom

Terminology

- Compartmental and exponential models, which model the observed in vivo data, referred to as top down approaches.
- PBPK: a bottom-up, systems, approach.

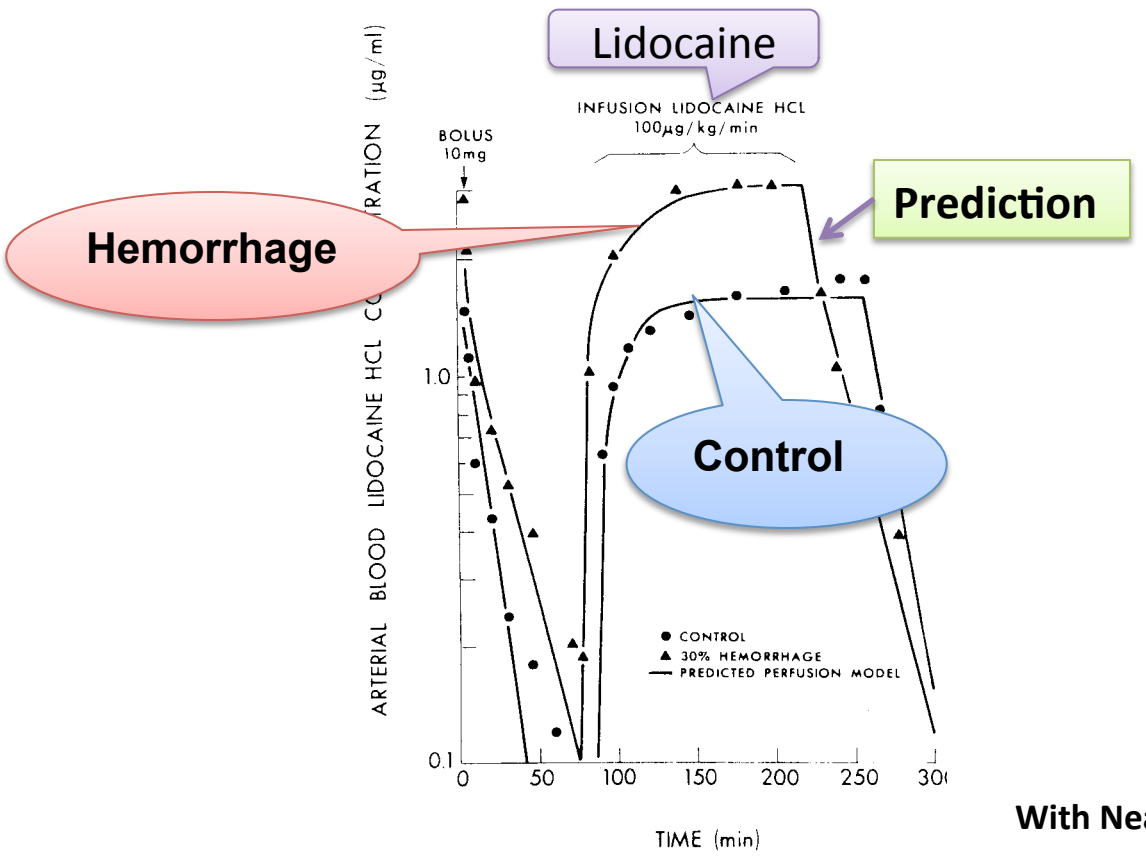
Stratagem within PBPK approach

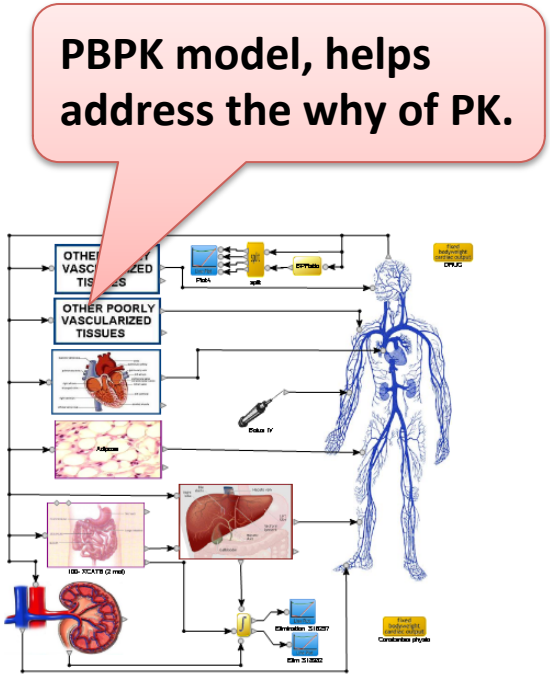
- Drug properties reside within the continuum of chemical and biological spaces



- Sparse data on a drug are made more useful by 'borrowing' information from biology and other drugs.
- (In POP-PK sparse data in an individual can made more useful by 'borrowing' information from other subjects).

Effect of hemorrhagic shock on pharmacokinetics

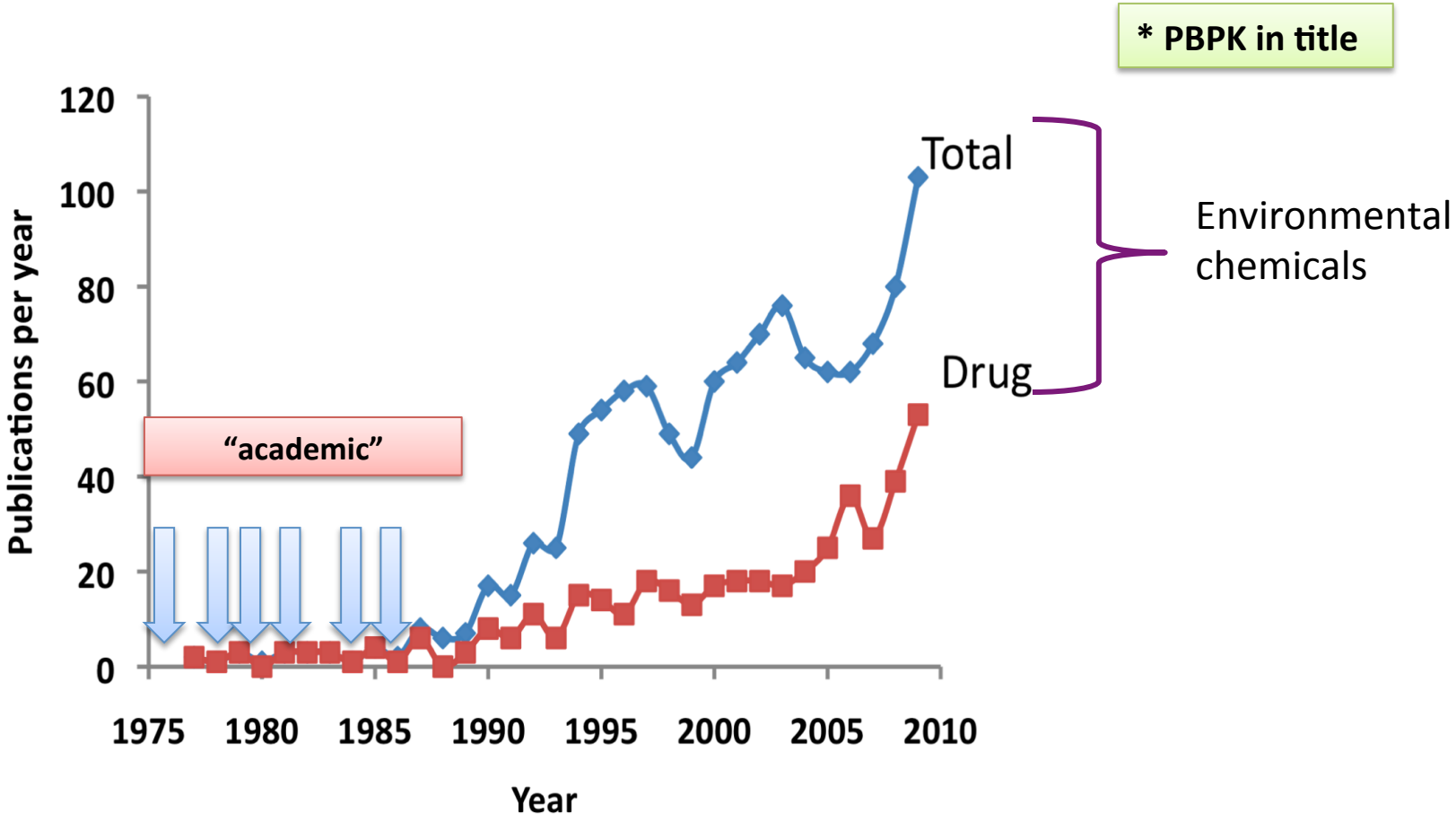




With Neal Benowitz, Ken Melmon

Ralph Forsyth Clin. Pharm. Therap. 1974

PBPK Publications*

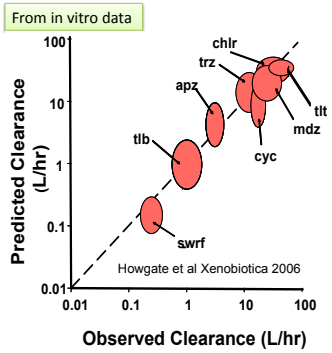


- Rowland, Peck, Tucker. Physiologically based pharmacokinetics: Applications to Drug Development and Regulatory Sciences. *Ann. Rev. Pharmacol. Toxicol*. 51, 45-73, 2011

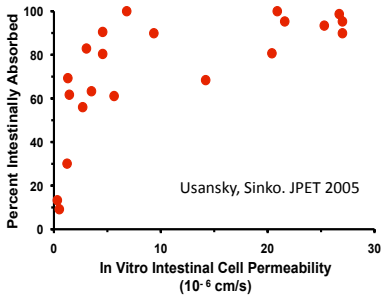
Factors revolutionizing application of PBPK > 1985

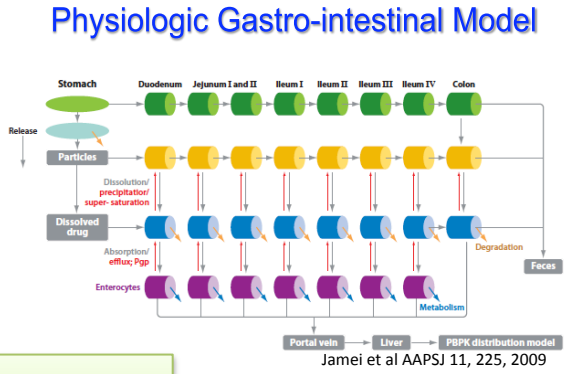
Improved molecular/mechanistic understanding of the processes: elimination and absorption

Physiologic models incorporating this information coupled with physicochemical and in vitro human drug data permitting increasingly accurate in vitro/in vivo extrapolation (IVIVE)



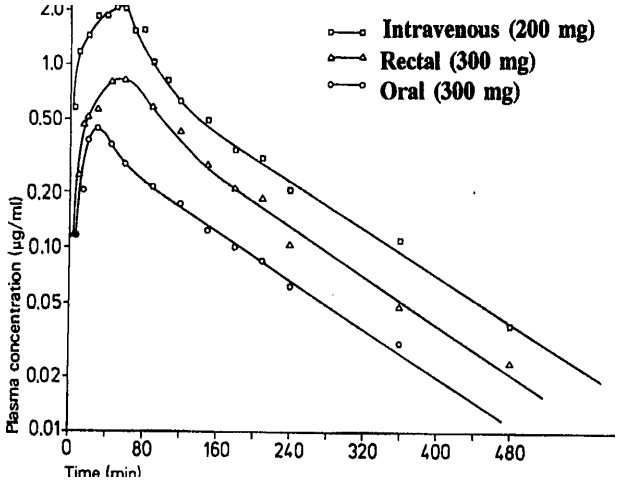
clearance



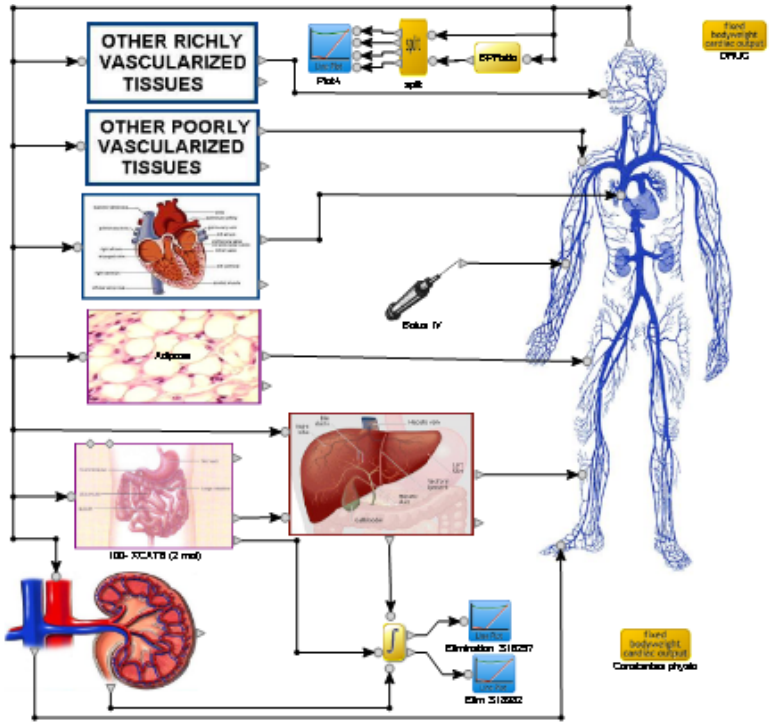


Intestinal absorption

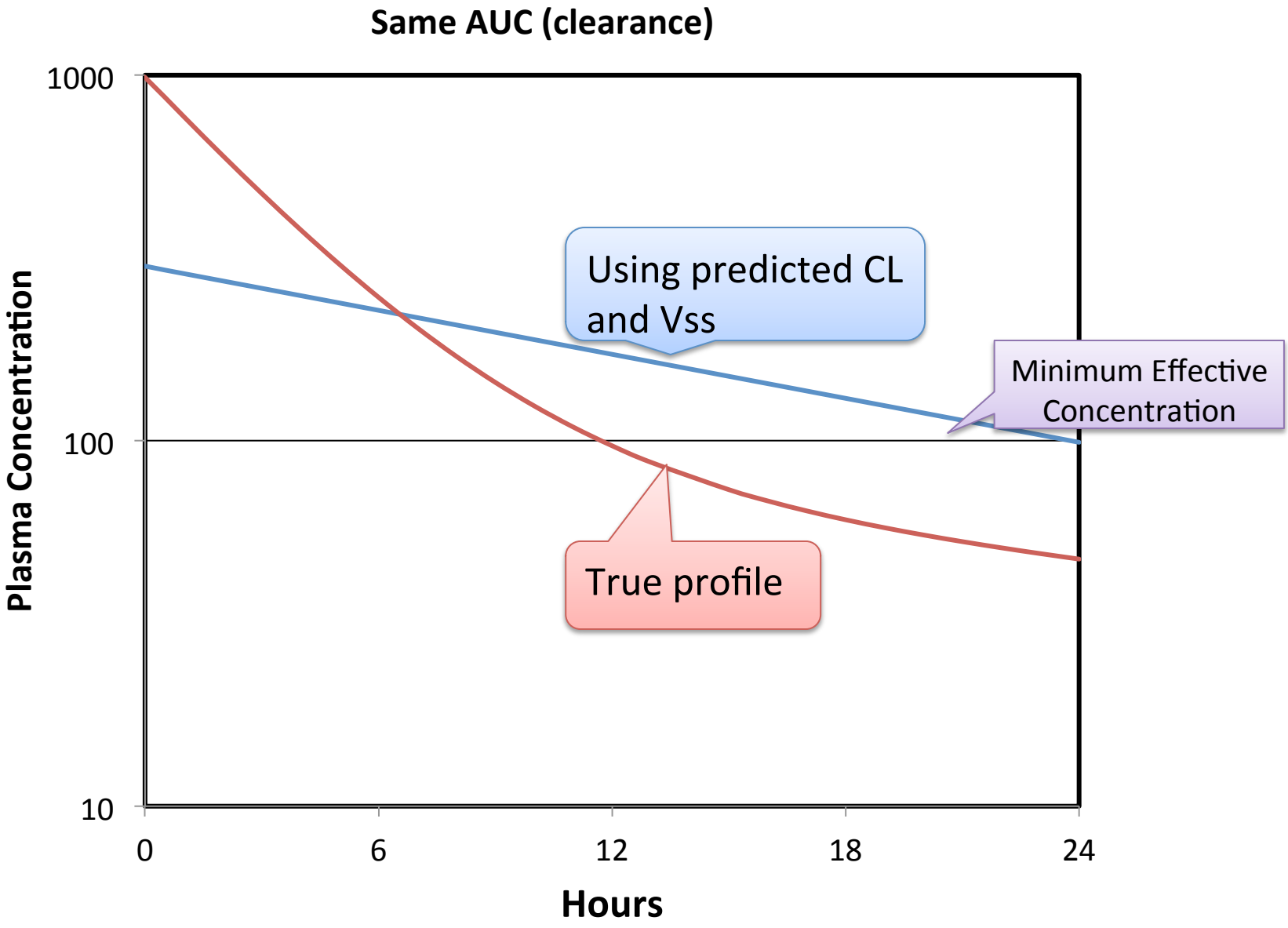
Tissue Distribution: a critical factor



Observed conc-time profile function of interaction of drug as it passes through each tissue and recirculation



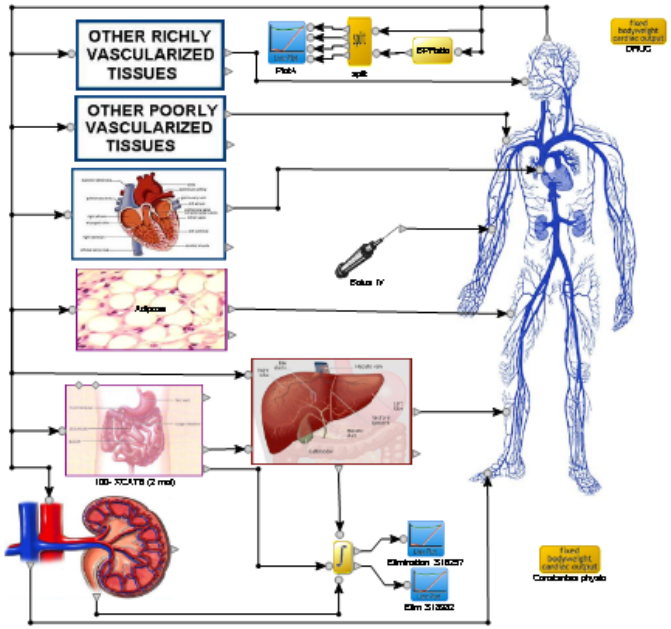
Shape is important



Determined
in vitro

Enzyme,
Transporter
Activity (CL_{int})
Permeability
PhysChem Prop

Plasma
Protein
Binding



Conventionally –
in vivo
Major impediment to implementation of PBPK approach

Tissue distribution

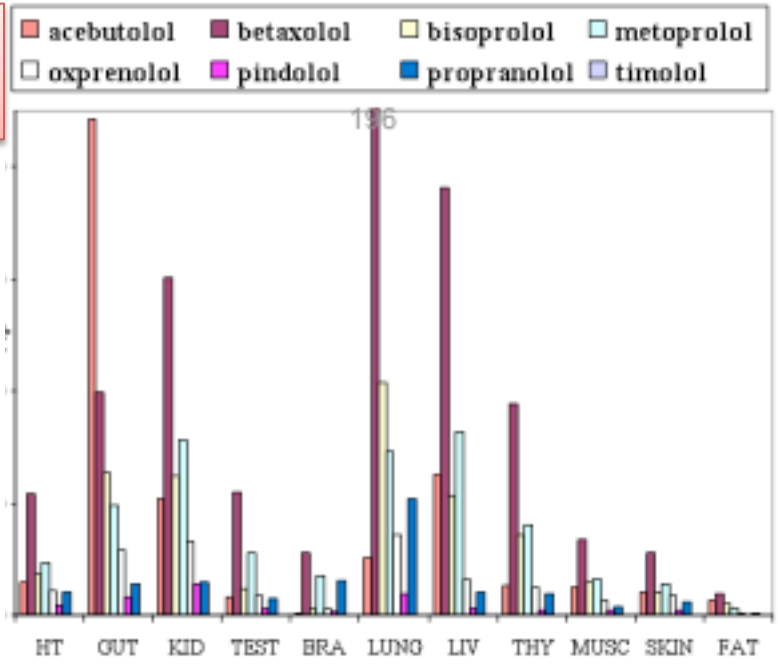
Literature

Tissue Weights,
Blood Flow, etc

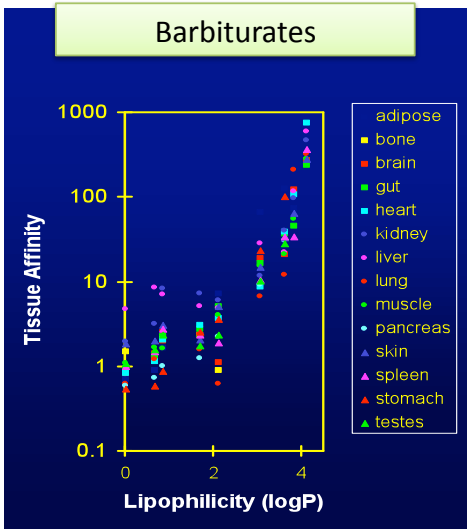
Lessons learnt from series

β-blockers

Tissue Affinity



Barbiturates



Toon et al. J. Pharmacol. Exptl. Therap., 225, 752 (1983)

Nestorov et al. J. Pharmacokin. Biopharm. 26, 521 (1998).

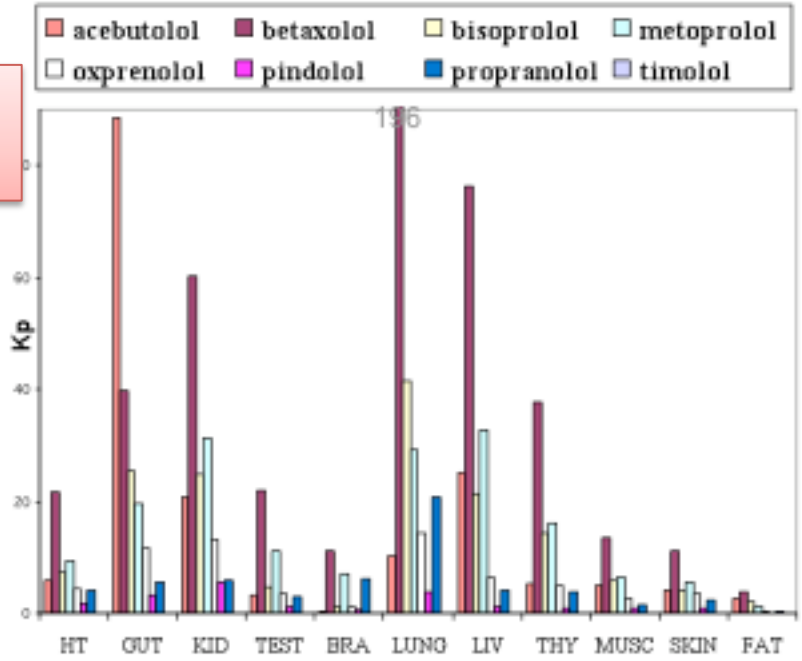
Why such wide variability among tissues in affinity for drugs, and between drugs for a tissue?

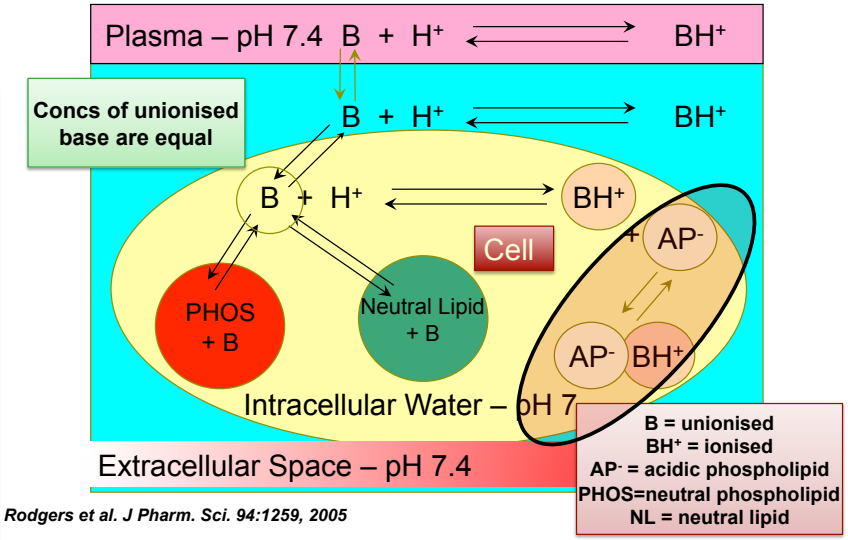
Composition helps explain the why of tissue distribution?

β-blockers

Tissue distribution model

Tissue Affinity

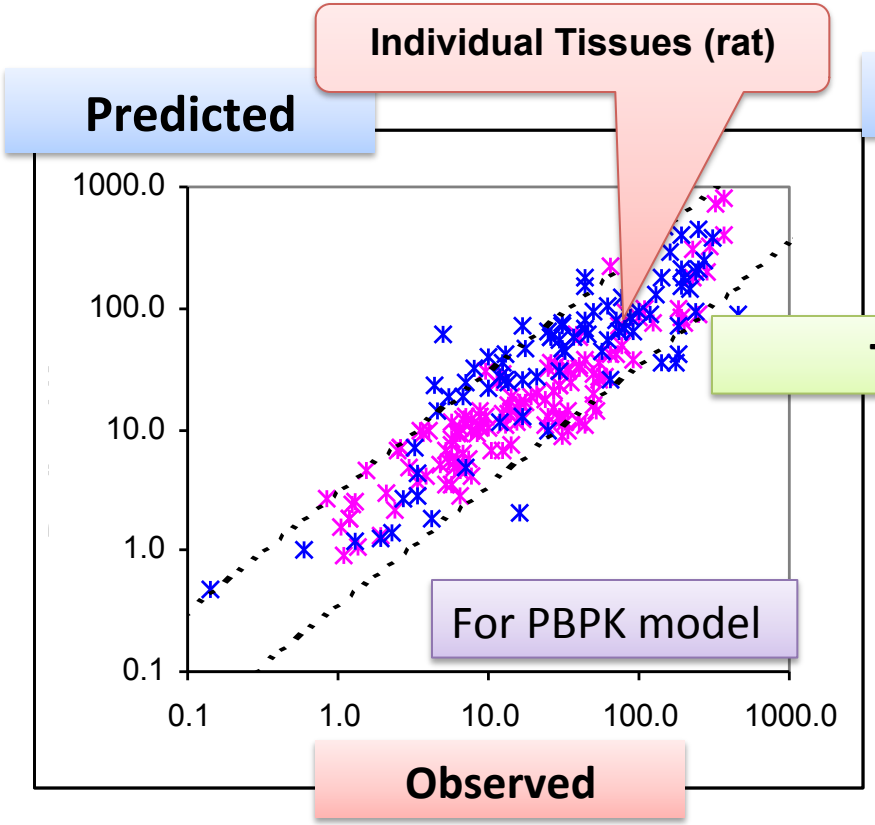




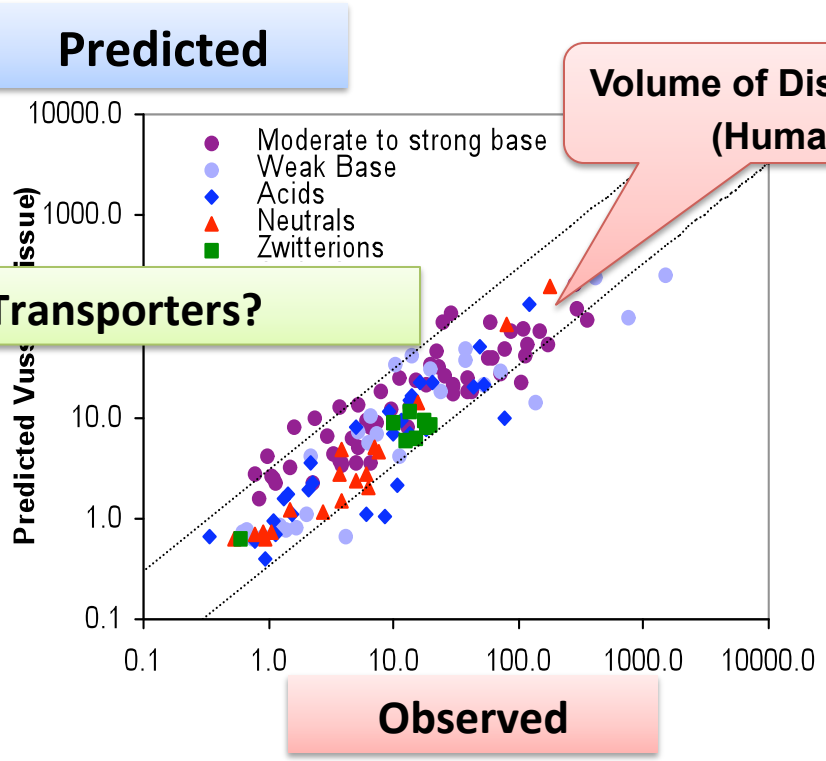
Rodgers et al. J Pharm. Sci. 94:1259, 2005

Wide variability among tissues in affinity for drugs

Model provides in silico prediction of tissue affinity from chemical drug properties and tissue composition.



Transporters?



Rodgers & Rowland. Pharm Res. May, 2007

Quality of Data: A critical factor

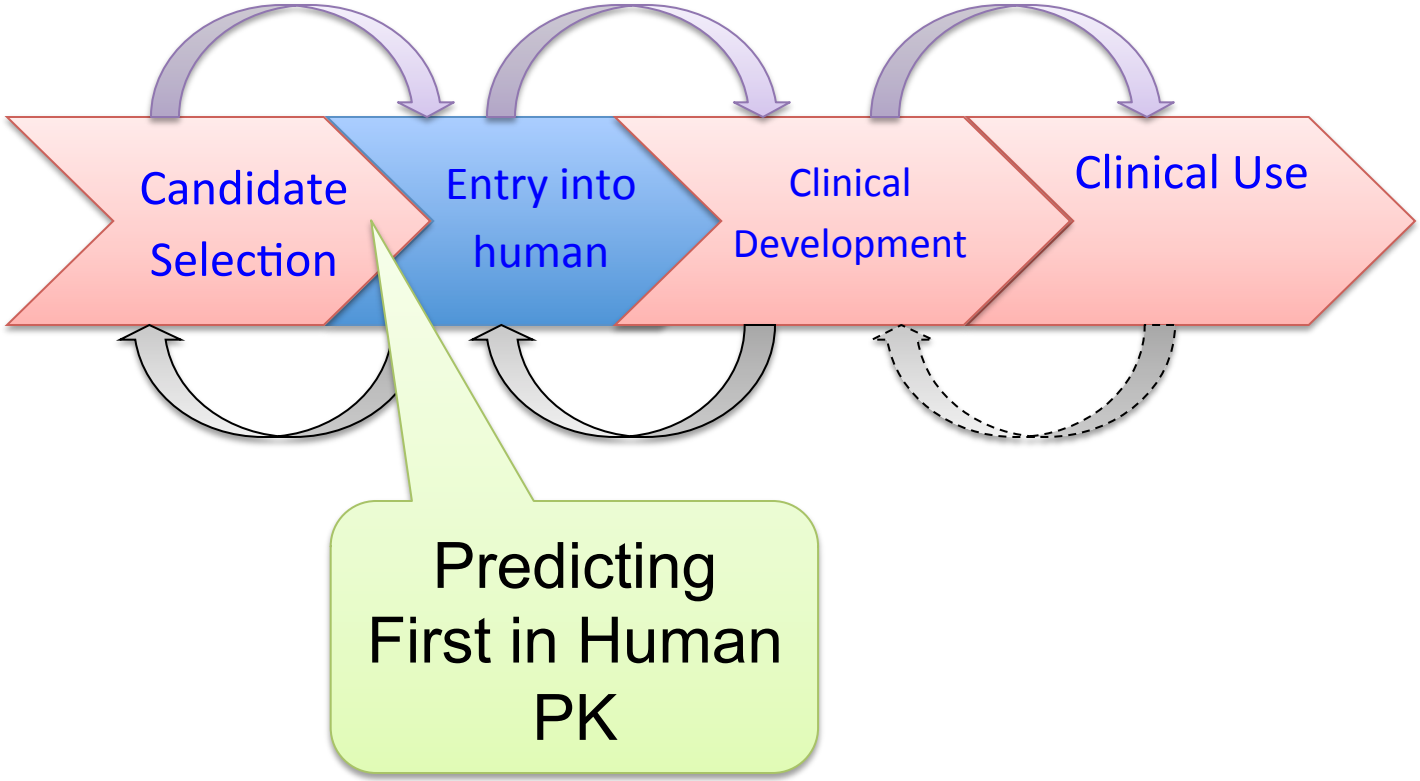
Prediction accuracy critically dependent on the quality of relevant in vitro and physicochemical data

Garbage in: garbage out

Further factors accelerating application of physiologically based PK

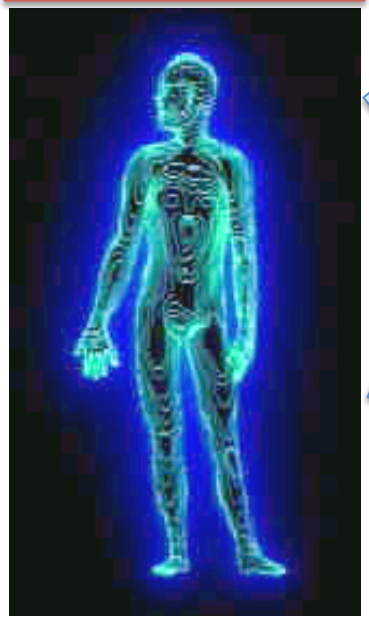
- Powerful, commercially available PBPK software platforms, incorporating all physiological, biochemical and other data relevant to needs of drug developers
- Receptivity of regulators (IND, NDA) submissions)

Adding value to drug selection, development, and use



Tackling the problem of preclinical human prediction

Prediction

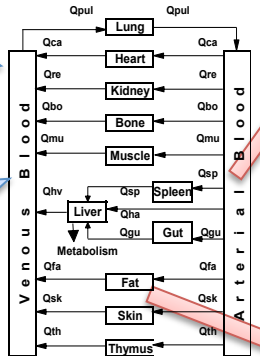


Enzyme & Transporter Activity, permeability etc

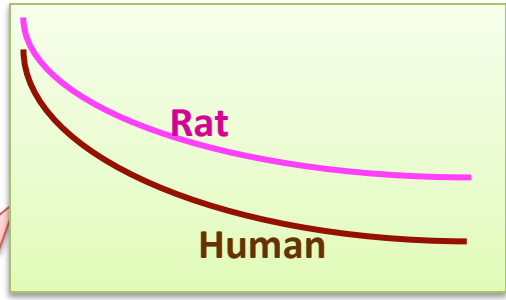
Protein Binding

Tissue Affinity

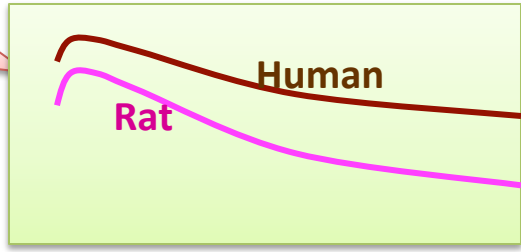
Tissue Weights, Flow



BLOOD



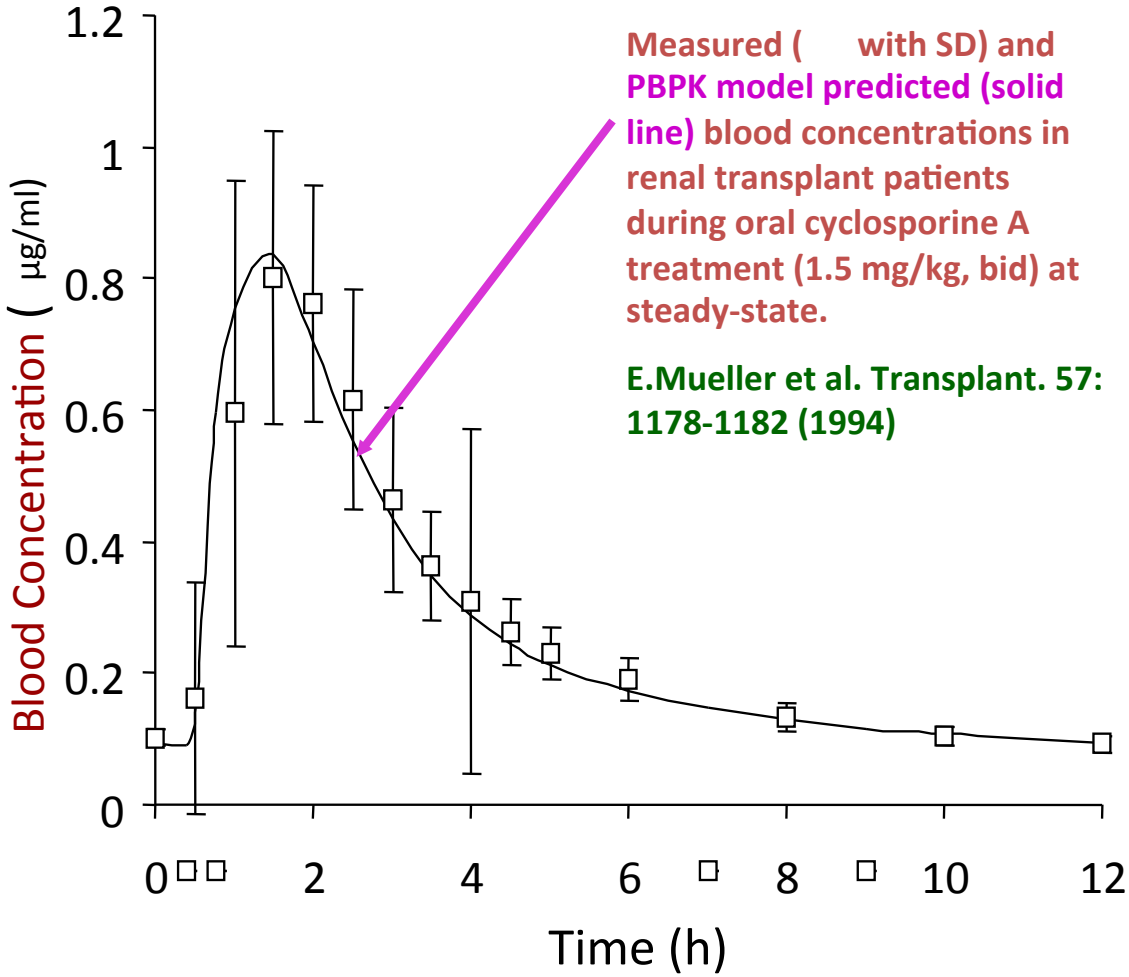
ADIPOSE



Some companies only use PBPK after verification in animals (rat)

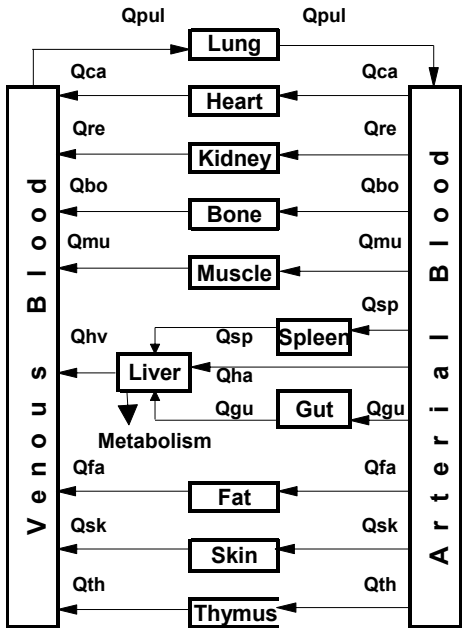
Prediction of human kinetics by PBPK model

Cyclosporin



Measured (with SD) and PBPK model predicted (solid line) blood concentrations in renal transplant patients during oral cyclosporine A treatment (1.5 mg/kg, bid) at steady-state.

E.Mueller et al. Transplant. 57: 1178-1182 (1994)

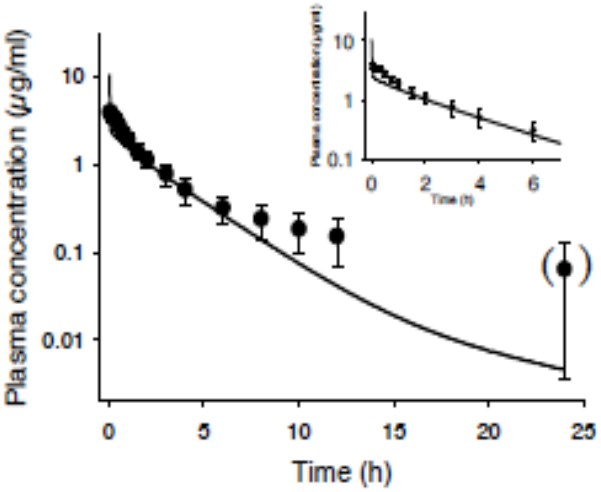


Kawai et al J. Pharmacol. Expt. Therap. 287: 457 (1998).

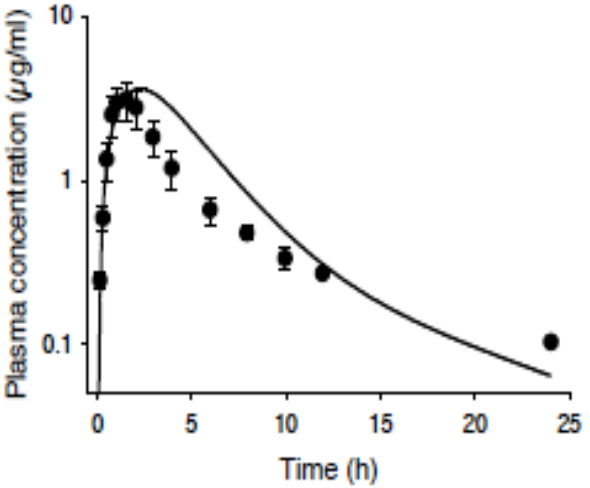
Valsartan: Human PBPK prediction

(Nonmetabolised, transport dependent)

Intravenous



Oral

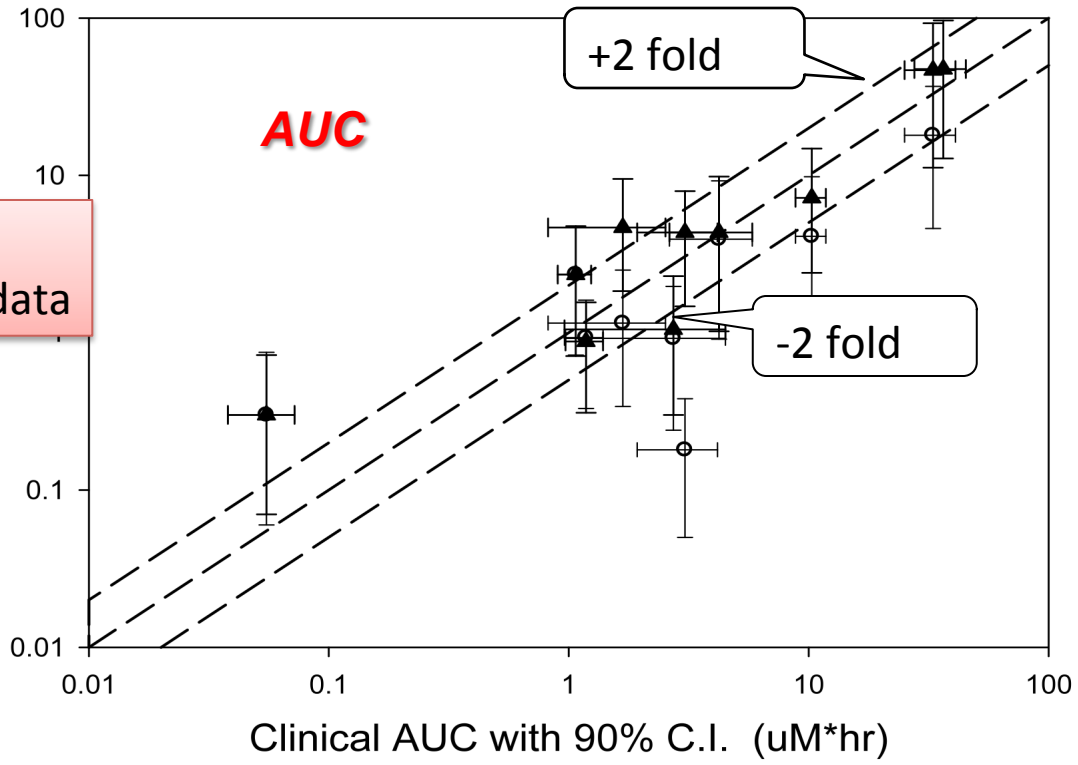


Poirier et al. J Pharmacokin. Pharmacodyn. 2009

Prediction of first in human PK

MW (g/mol)	cLog P	Dose (mg)
495.6	-0.17	60
457.5	3.4	5
444.4	4.0	160
467.5	2.4	1
380.4	3.9	3
338.4	1.7	125
458.5	4.2	120

Prediction based only on physicochemical and in vitro human data



Gibson, et al. Xenobiotica 39:637-48, 2009

Plasma Concentrations FIH Predictions

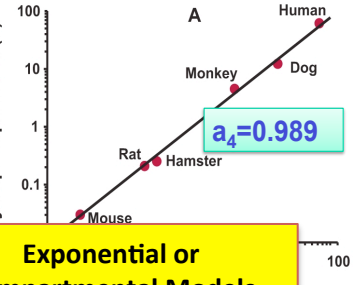
Roche Experience

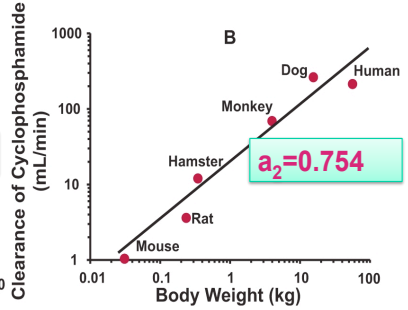
Volume of Distribution

Clearance

Scaling based on Body Weight

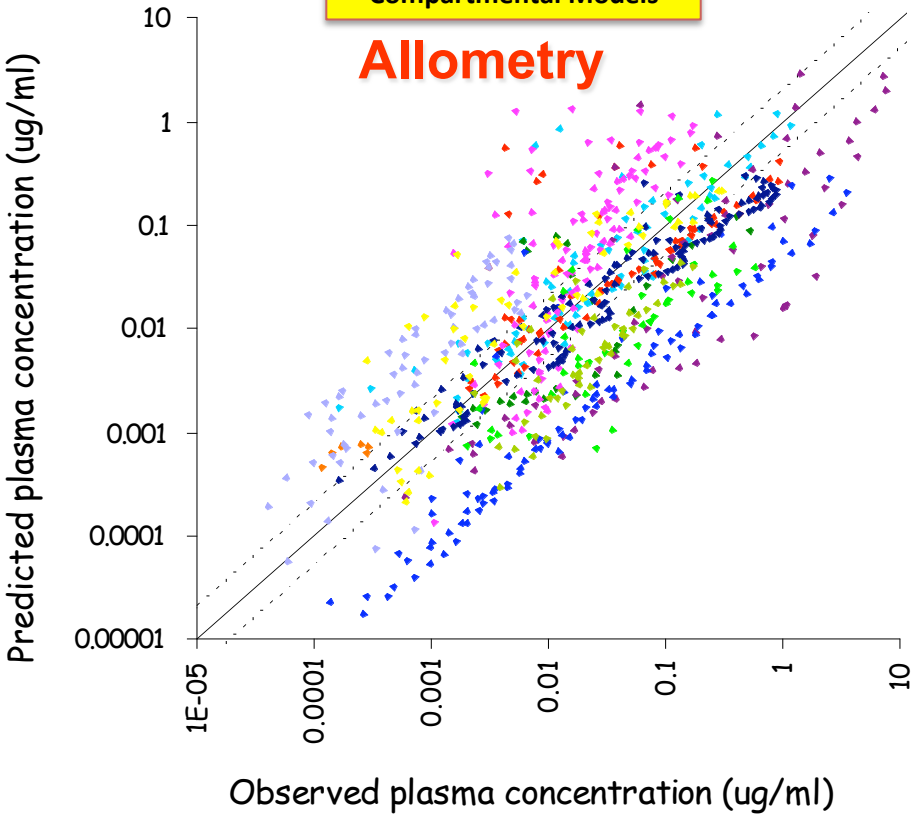
Assume that CL,V scale to body weight.



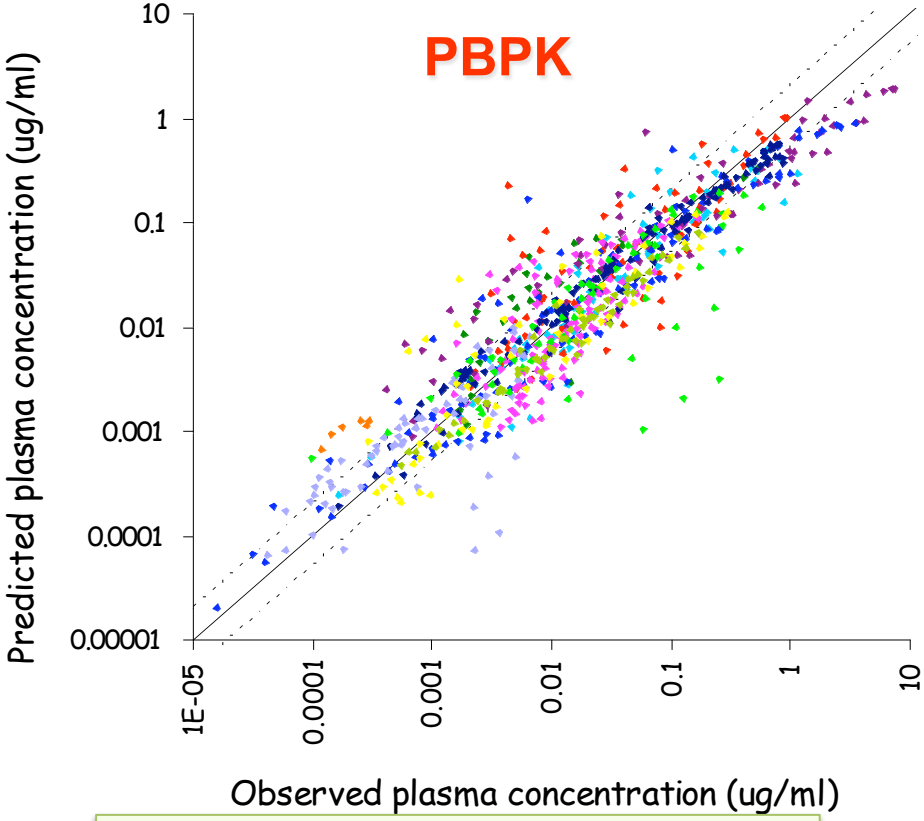


Exponential or Compartmental Models

Allometry



PBPK

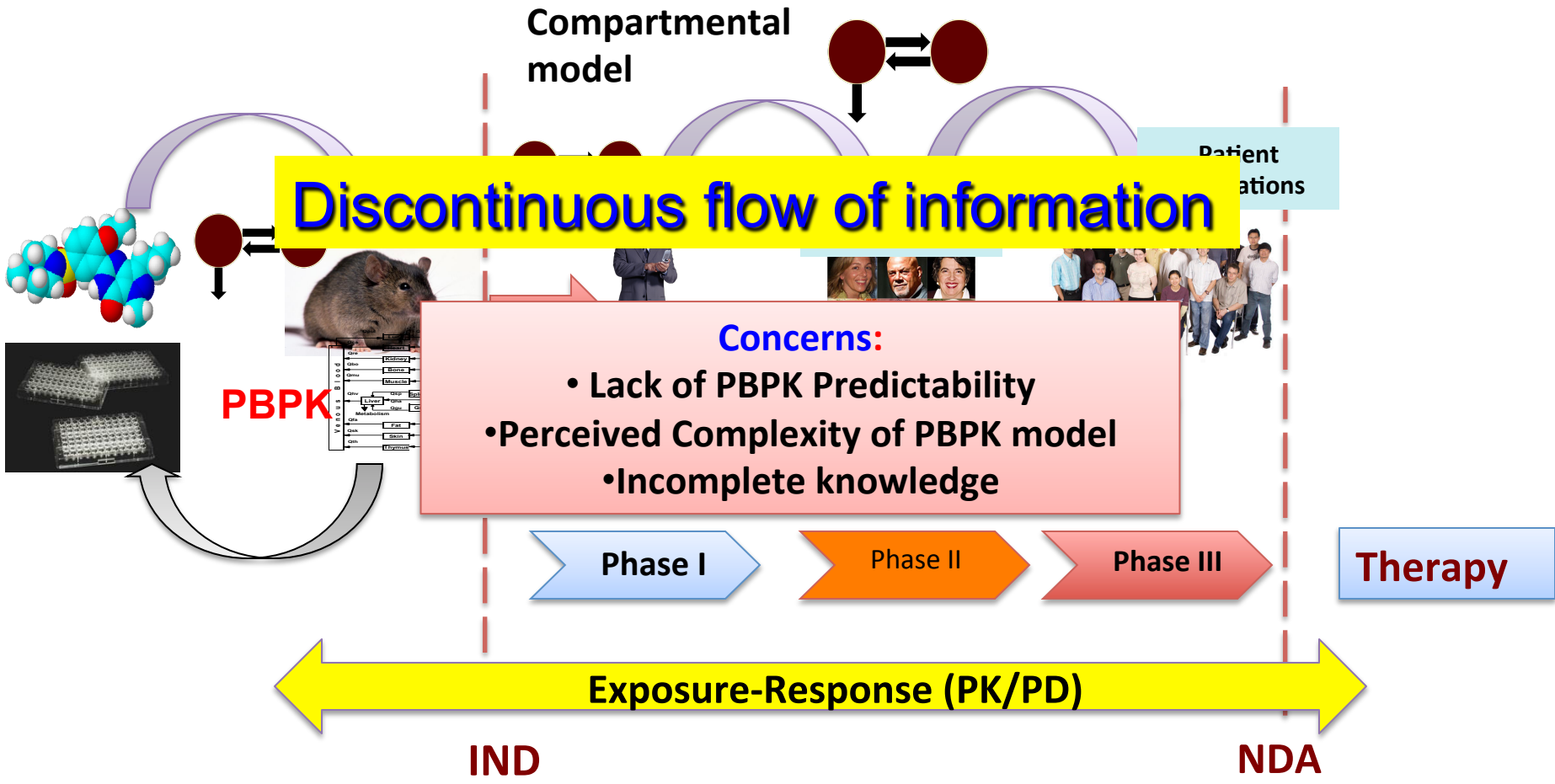


Rowland, Peck, Tucker *Ann. Rev. Pharmacol. Toxicol.* 51, 45, 2011

Allometry

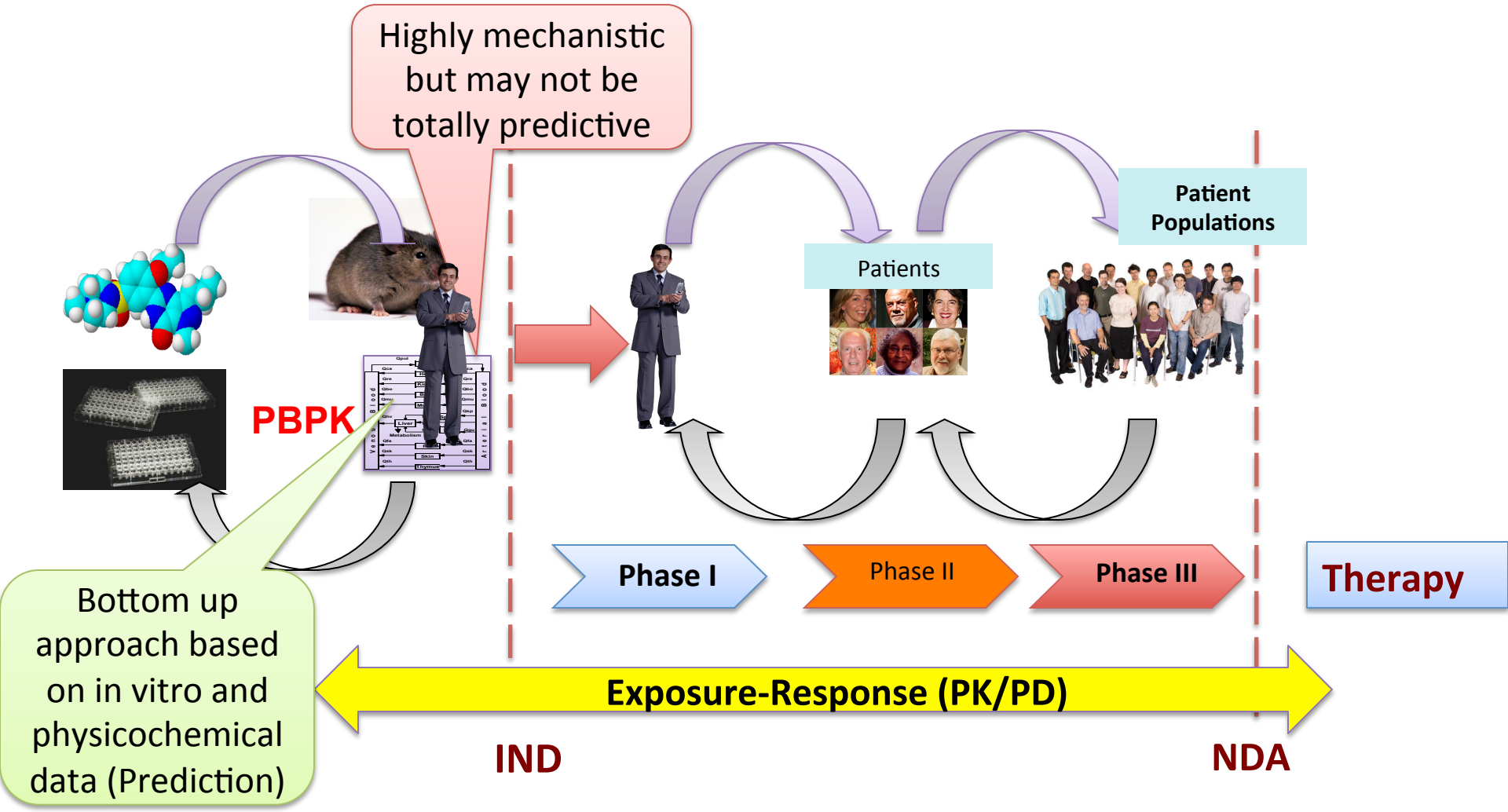
- Cannot predict in humans influence of
  - Age
  - Sex
  - Genetics
  - Disease
  - Drug Interactions
  - ……

Current PK paradigm in Drug Development

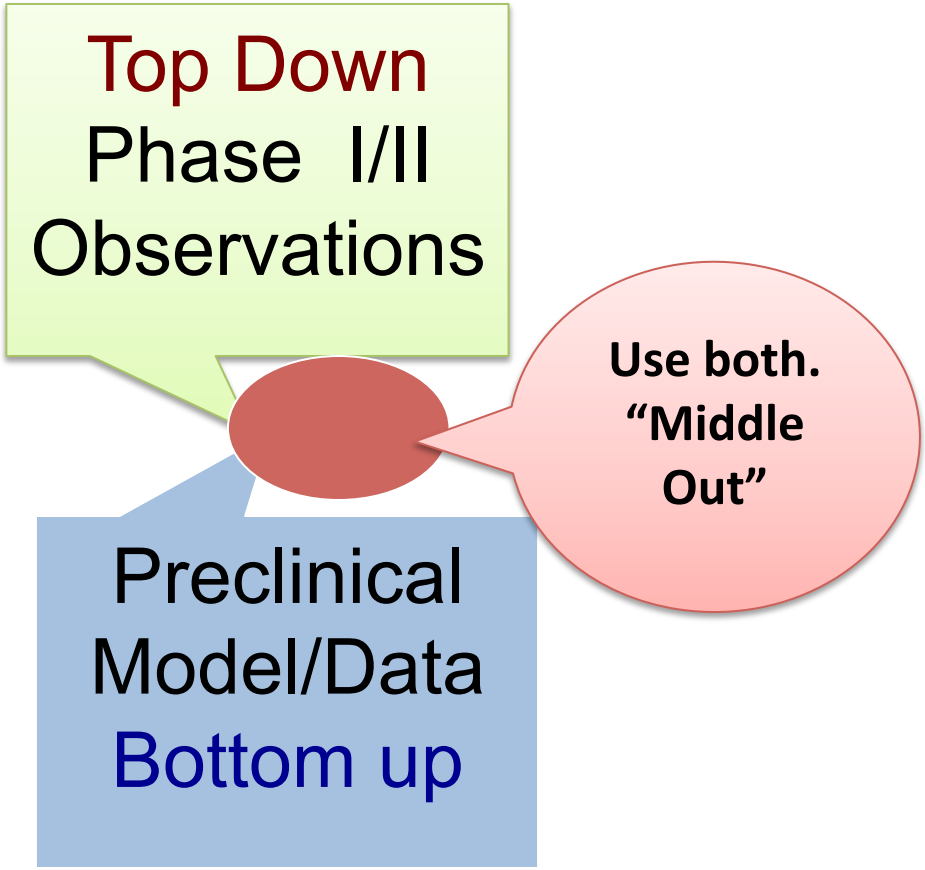


Gueorguieva et al J. Pharmacokin. Pharmacodyn 33:571-594 (2006)

Increasingly common PK paradigm in Drug Development



Need to integrate Phase I/II clinical data with preclinical PBPK model/data

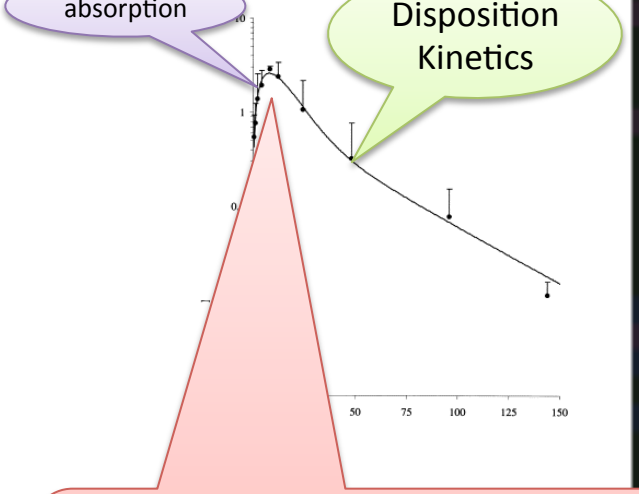


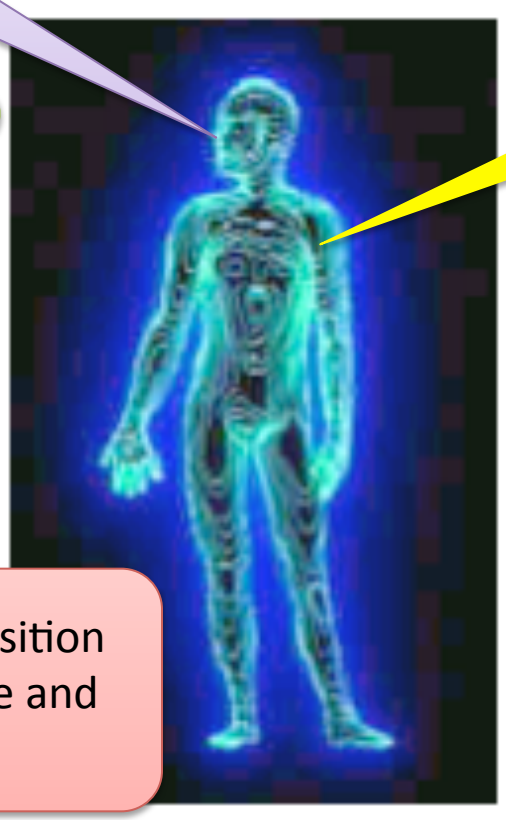
Updating the PBPK model: a strategy

Oral (extravascular) administration

absorption

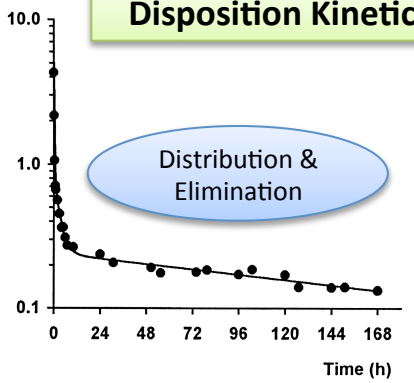
Disposition Kinetics





Intravenous administration

Disposition Kinetics



Distribution & Elimination

Need to separate out disposition kinetics to characterise rate and extent of absorption

Jones et al. Clin. Pharmacokin. 50: 331, 2011

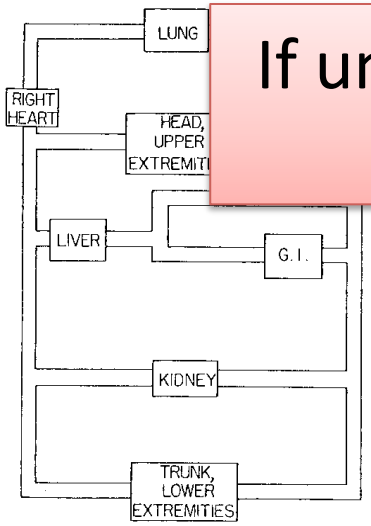
Intravenous PK

- iv Microdose (Subpharmacologic, ≤ 100 µg; Phase 0, given alone, before FIH), or
- iv 'light' (< 200 nC) tracer given simultaneously with oral therapeutic dose.
- Most cases, PK behaviour virtually identical
- Also, often oral microdose predicts oral therapeutic dose

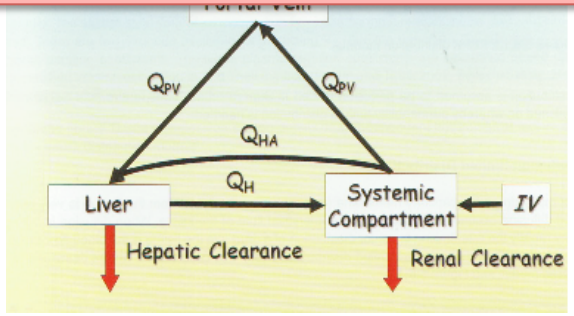
Rowland. Microdosing commentary, J. Pharm. Sc, November Issue, 2012

Model Complexity: Reduction

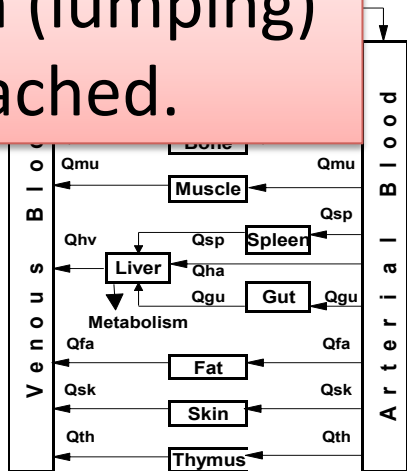
If undertaken model reduction (lumping) should be formally approached.



'Minimammal' model of Bischoff & Brown, 1966



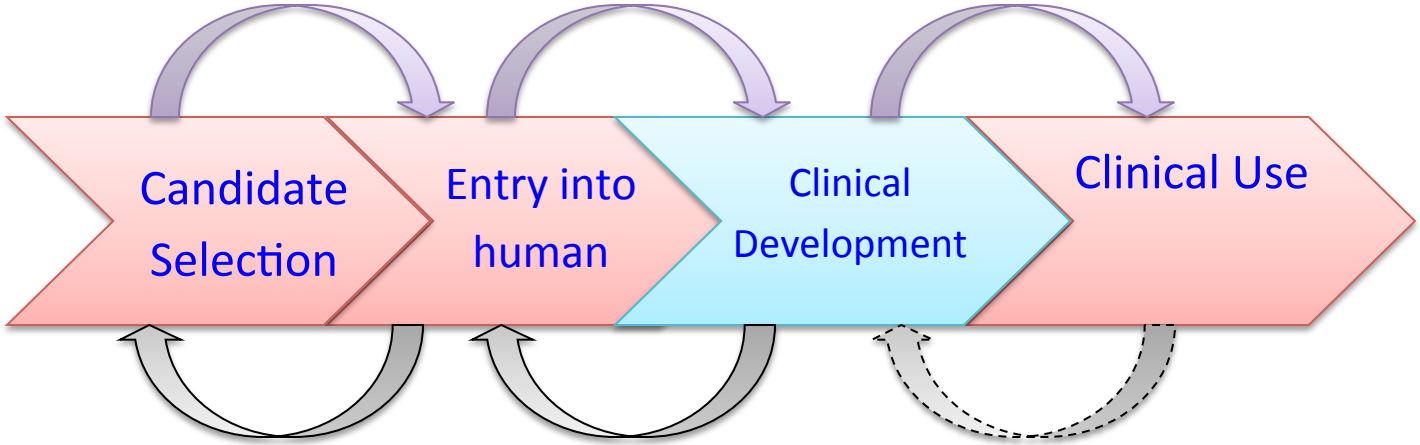
Minimum PBPK Model
Yeo et al 2010



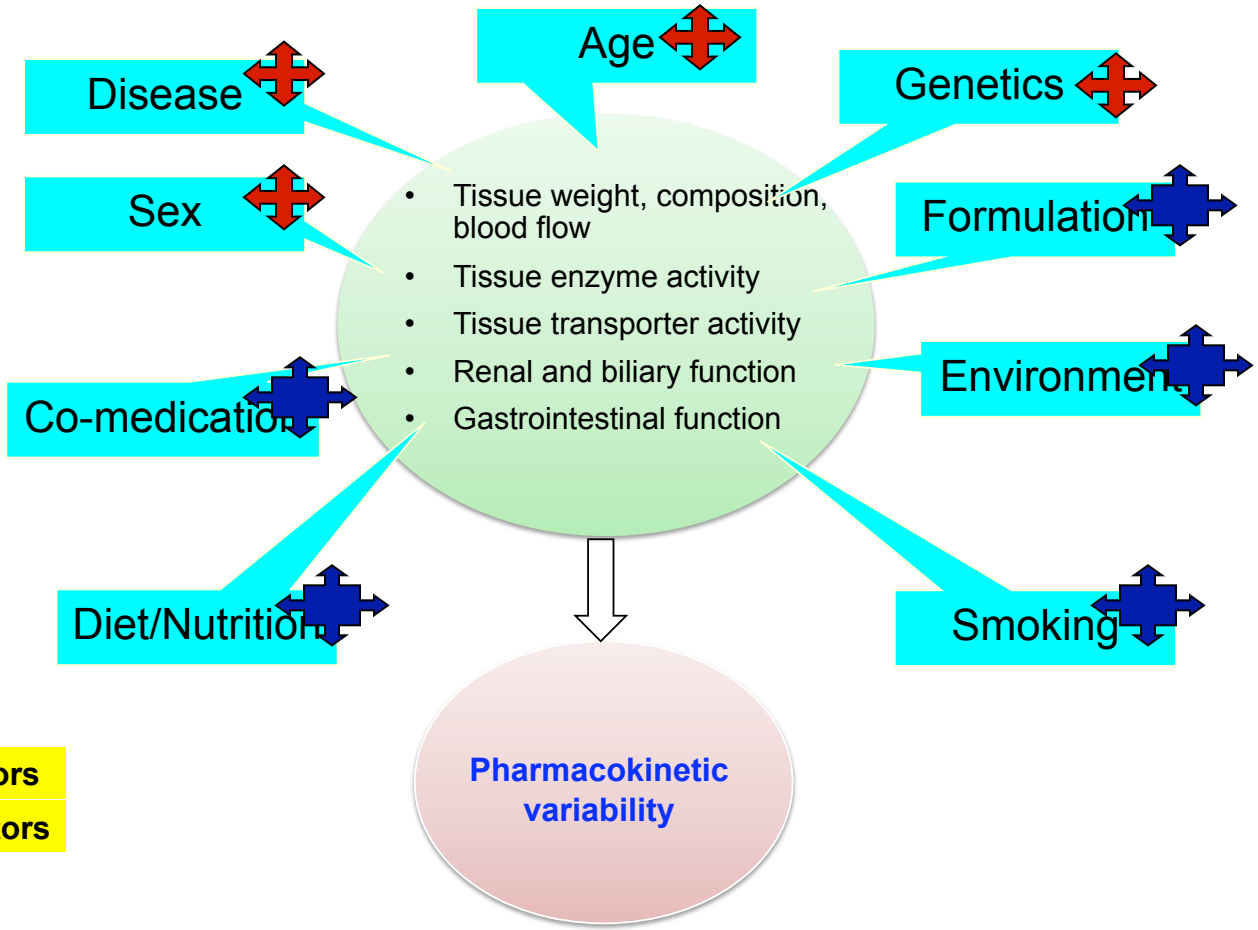
'Full' PBPK Model

Gueorguieva, et al *J. Pharmacokin. Pharmacodyn.* **33**: 1 (2006).

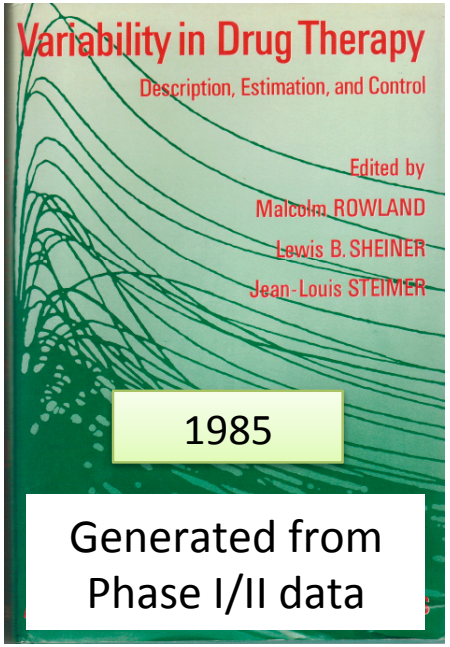
Adding value to drug selection, development, and use



PK Variability



Simulating *a priori* PK variability

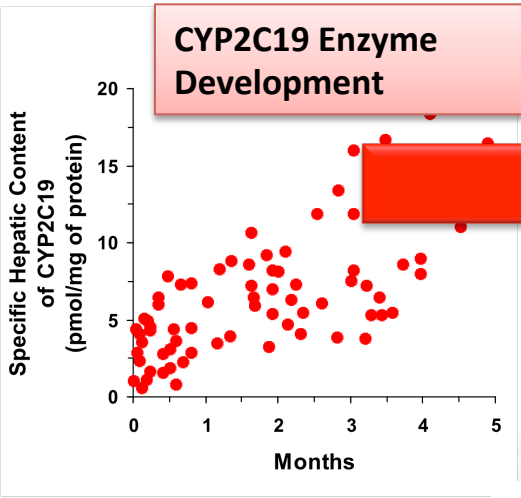


Generated from Phase I/II data

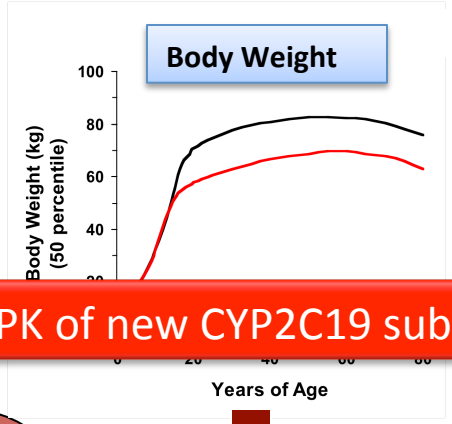
- Much now known about what contributes qualitatively and quantitatively to PK variability
- At typical doses many drugs reflect (and do not perturb) the 'state' of an individual
- So, knowing the 'state' allows prediction of an individual's PK

Drugs PK tend to reflect Independent Variables

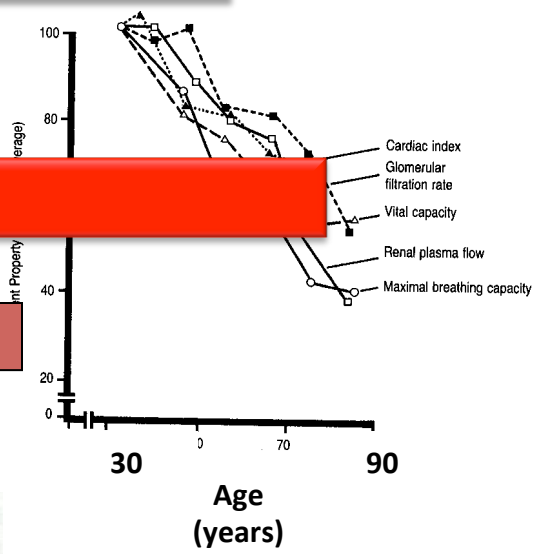
CYP2C19 Enzyme Development



Body Weight

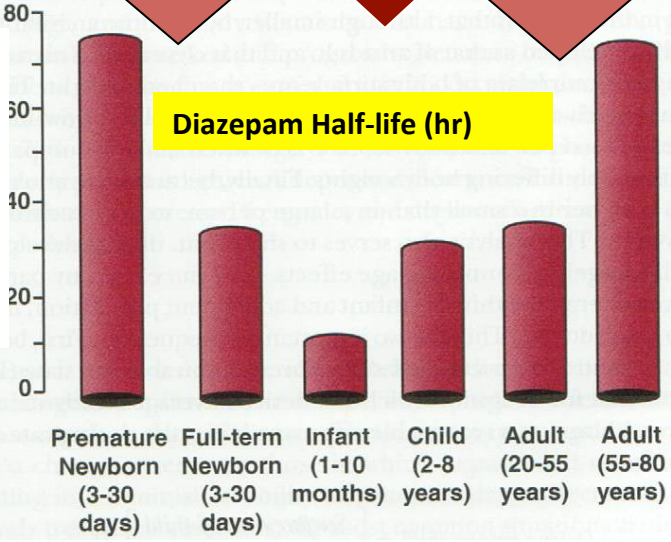


% Function Remaining

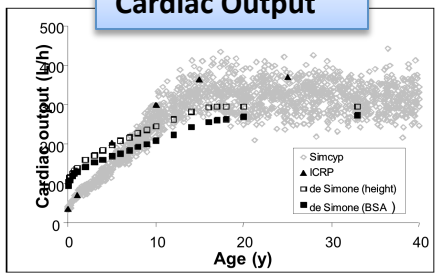


PK of new CYP2C19 substrate?

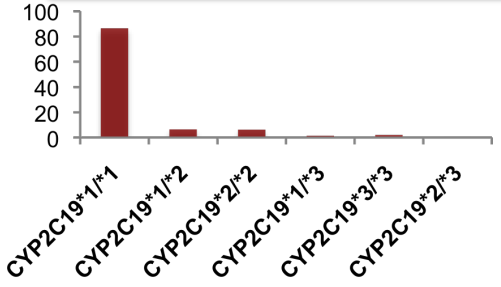
Diazepam Half-life (hr)



Cardiac Output



CYP2C19 Allele Frequency



Tackling the problem of simulating likely PK variability

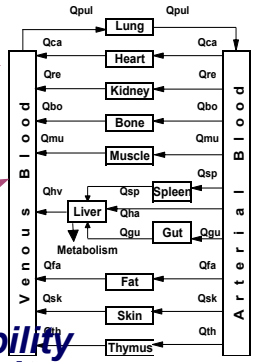
- Age
- Disease
- Drugs
- Genetics
- Sex
- Food
- Formulation
- Environmental

Enzyme & transporter Activity (CL_{int})

Protein Binding

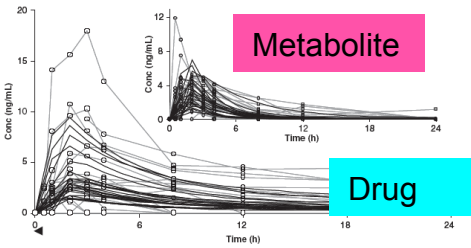
Tissue Permeability and Affinity

Tissue Weights, Flow, composition, etc



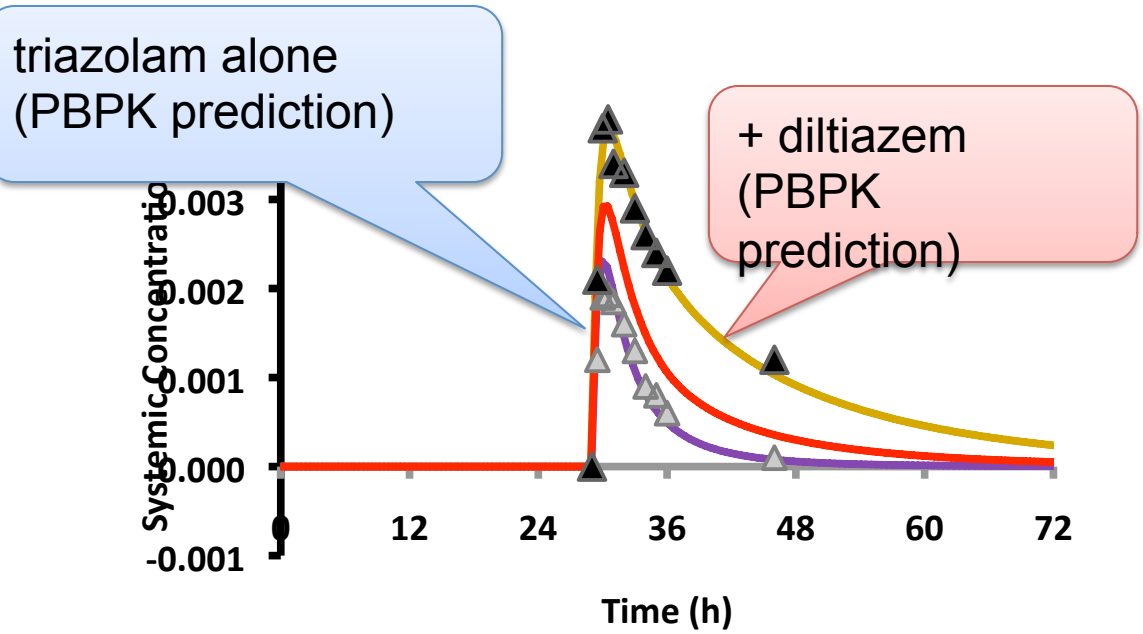
A bottom up approach

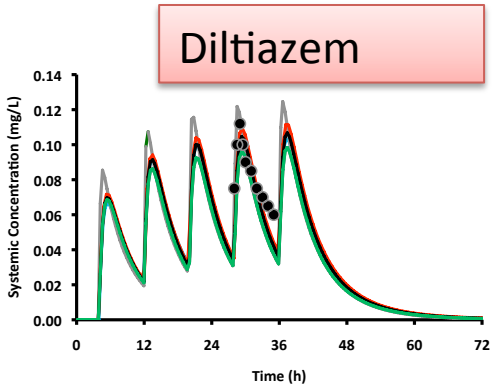
Dextromethorphan

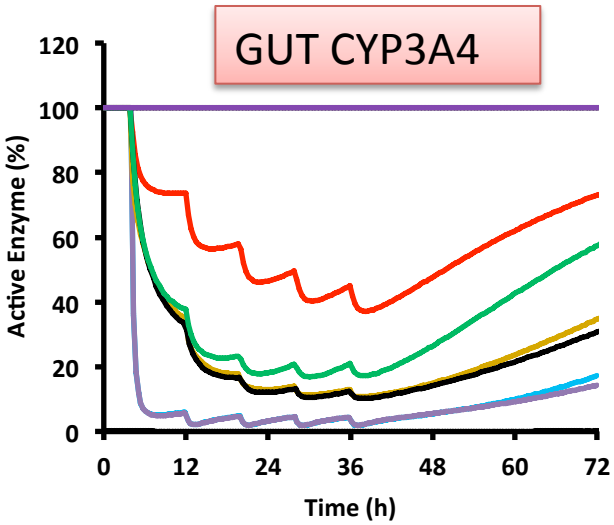


Dickinsen et al J Clin P'col 2007

DDI Prediction : e.g. Diltiazem-Triazolam Interaction



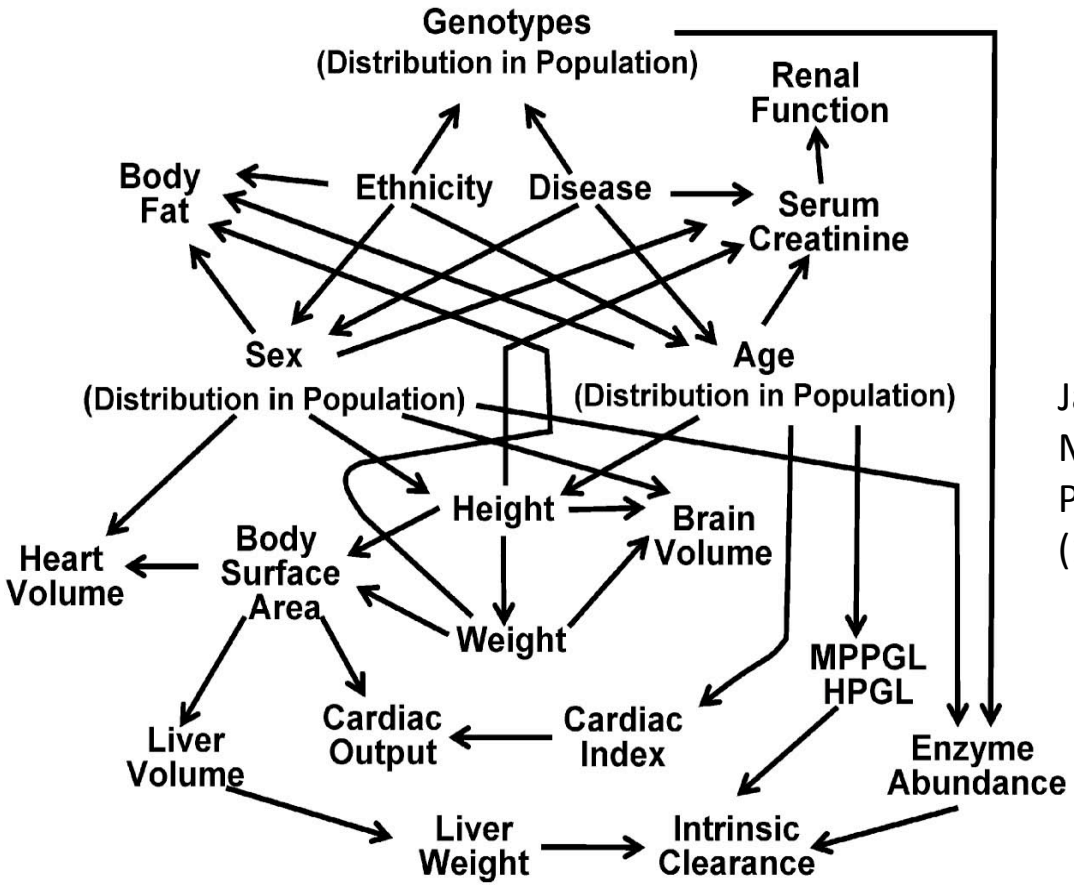




Rowland-Yeo et al. Eur. J. Pharm. Sci. 39:298–309

90+ yrs, frail

Multiple diseases, multiple drugs, declining weight, function etc

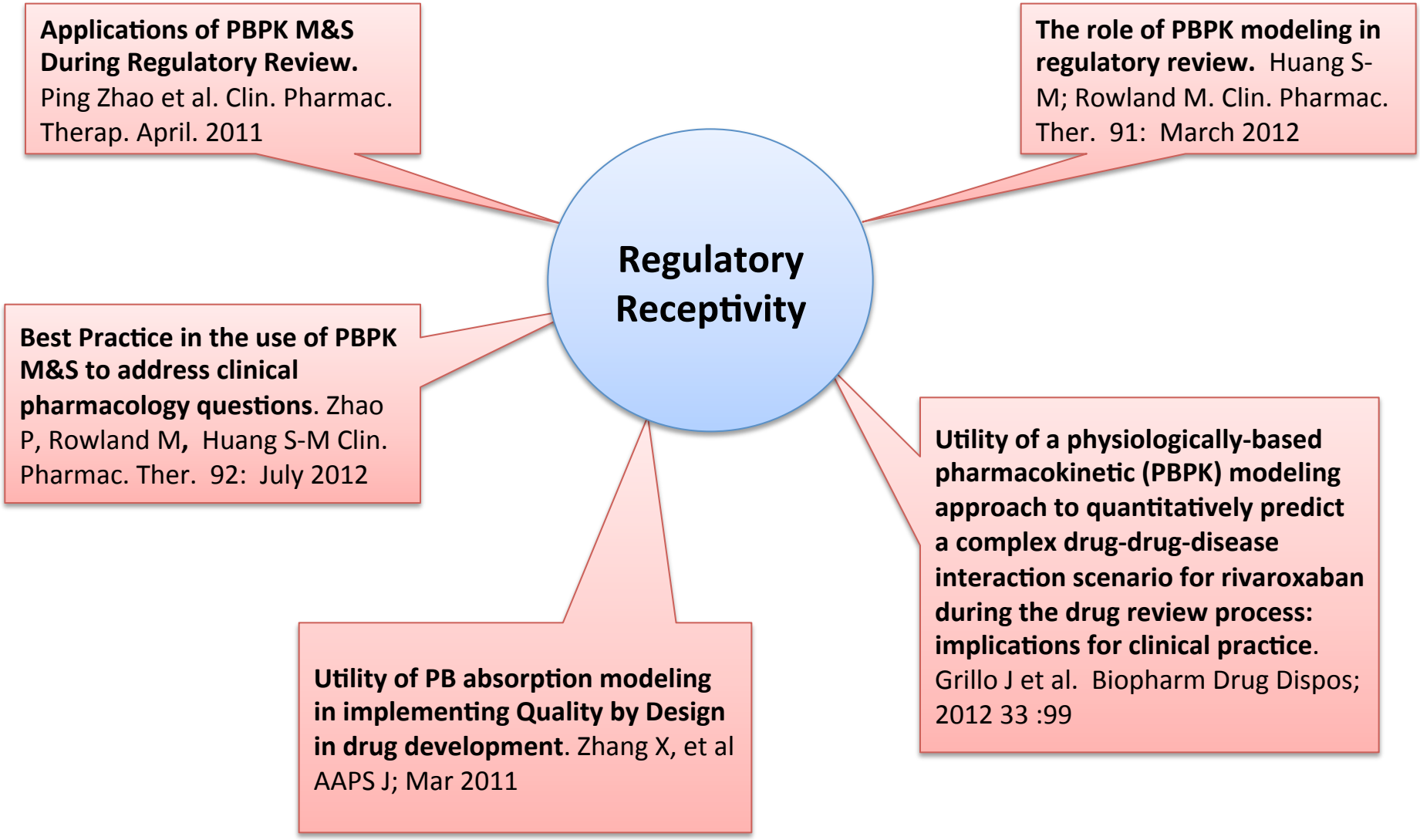


Jamel et al Drug Metab. Pharmacokinet. 24 (1): 53–75 (2009).

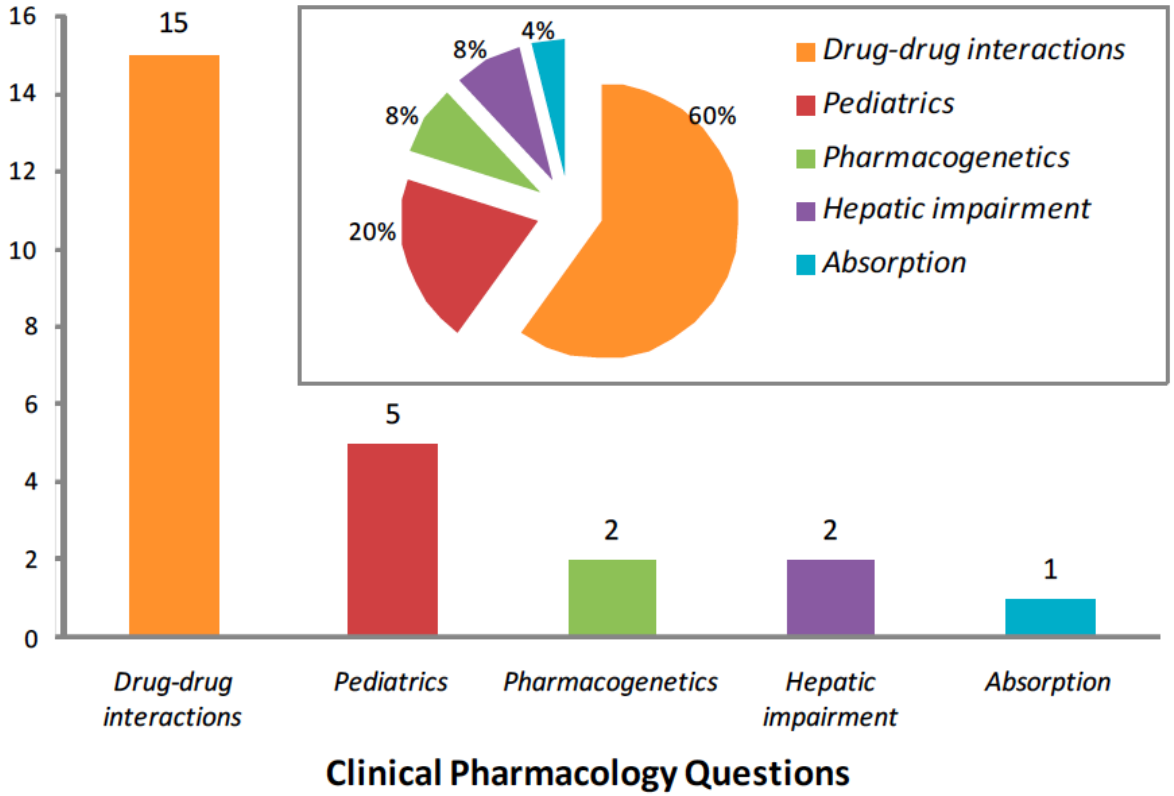
Many factors highly correlated. Often too complex to predict intuitively or empirically. Need a mechanistic model.

Experimental Design

Simulations of situations of interest help in the subsequent design of informative trials



Questions addressed by PBPK: FDA Submissions June 2008 – December 2011



Zhao, Rowland, Huang. CPT 92: 17-21, 2012

Some considerations

- Verification: show PBPK model able to predict independent data than used in initial model development eg fit adult data, including DDI etc, before pediatric application
- Sensitivity analysis: assess which parameters of the model most influence outcome.
- Model plausibility: if several, explain consequences of each in addressing questions
- Transparency of modeling: software, version, drug input parameters with source, etc

More informed labeling

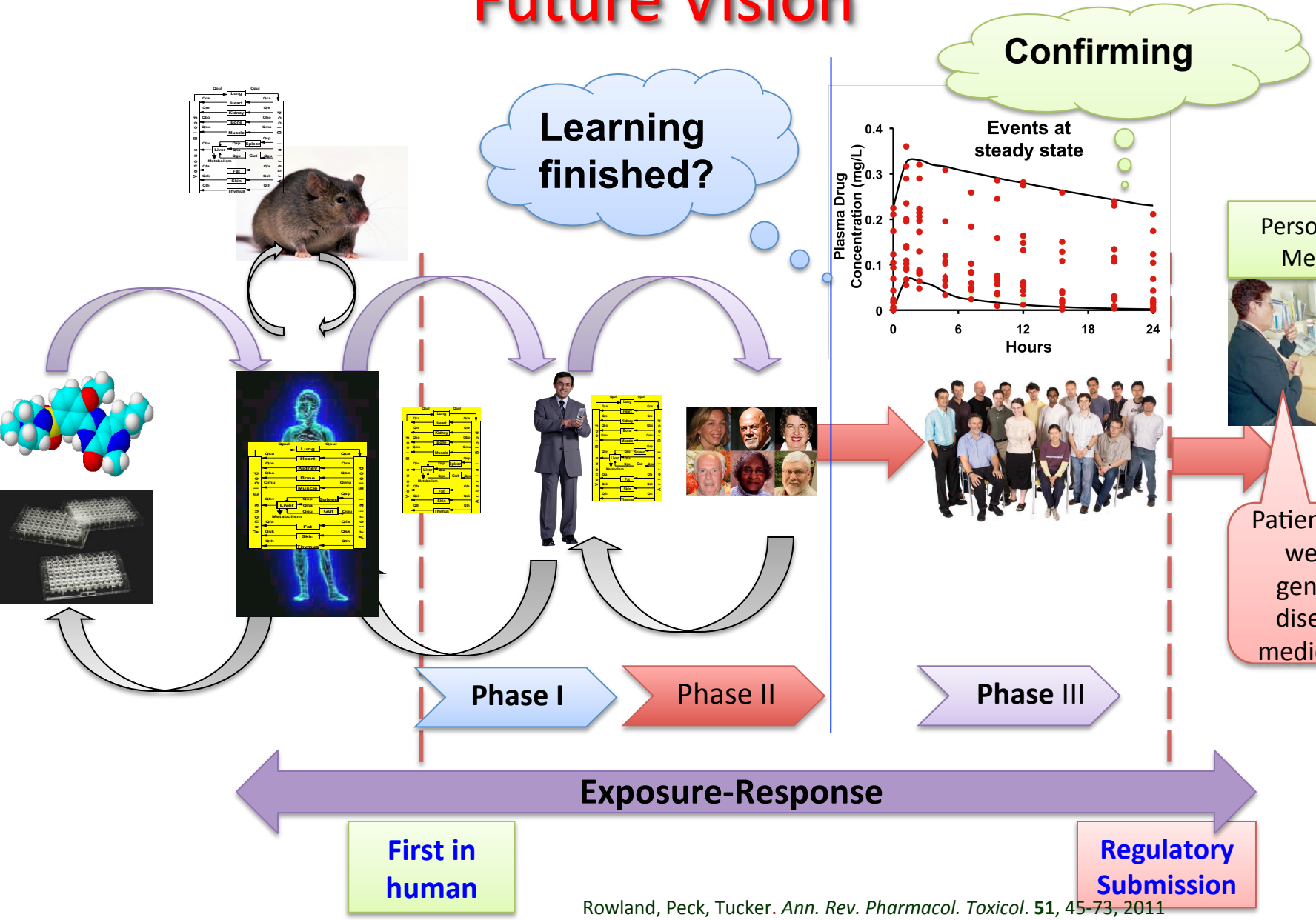
- Application of PBPK to make recommendations beyond Phase III studies, (which are still limited), e.g.,
  - Number and type of patients (many exclusion criteria) e.g. the very elderly frail, spectrum of patient characteristics on drug post marketing.
  - Conditions: Patients on 2-3 mild-moderate inhibitors of elimination pathways of drug, with renal impairment.

Learning vs. Confirming

- Learning goal = **making predictions**
  - Individualized doses, outcome probabilities
  - Efficient and effective trial designs
  - Requires *science* to generalize/extrapolate
- Confirming Goal = **testing predictions**
  - Safe (acceptable toxicity) and
  - Effective (adequate efficacy) for claimed indication
  - Requires *empiricism* to be believable to skeptics

From Lewis Sheiner's 2004 Oscar B Hunter Award Lecture

Future Vision



Rowland, Peck, Tucker. *Ann. Rev. Pharmacol. Toxicol*. **51**, 45-73, 2011

Concluding Remarks

- PBPK offers a mechanistic approach, with the potential for increased understanding and predictability during all phases of drug development
- Now increasingly possible with the availability of commercially supported software.
- In its early stages of industrial and regulatory application
- Room for improvement in the in vitro systems and some of the needed biologic information, including variability and correlation between covariates

PBPK: It can only get better

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