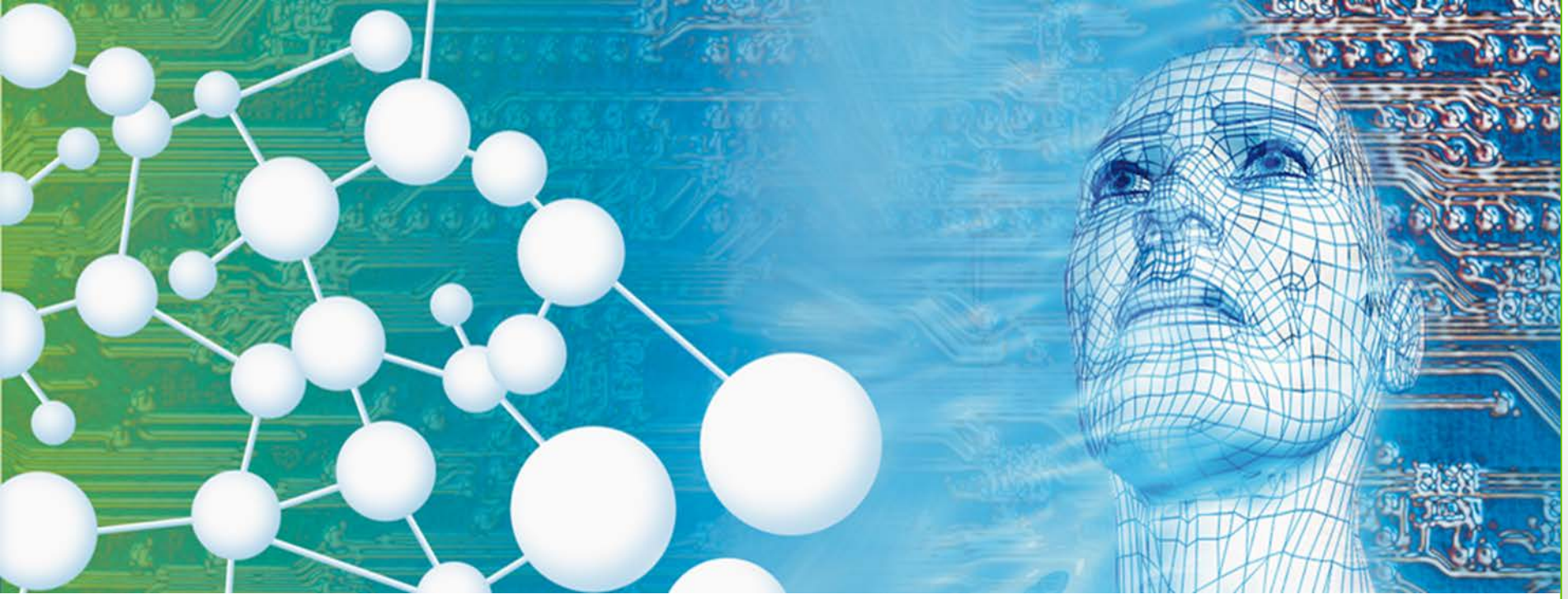


Science For A Better Life

PK-Sim 5 for Physiology Based PK modelling

Introduction and Demonstration

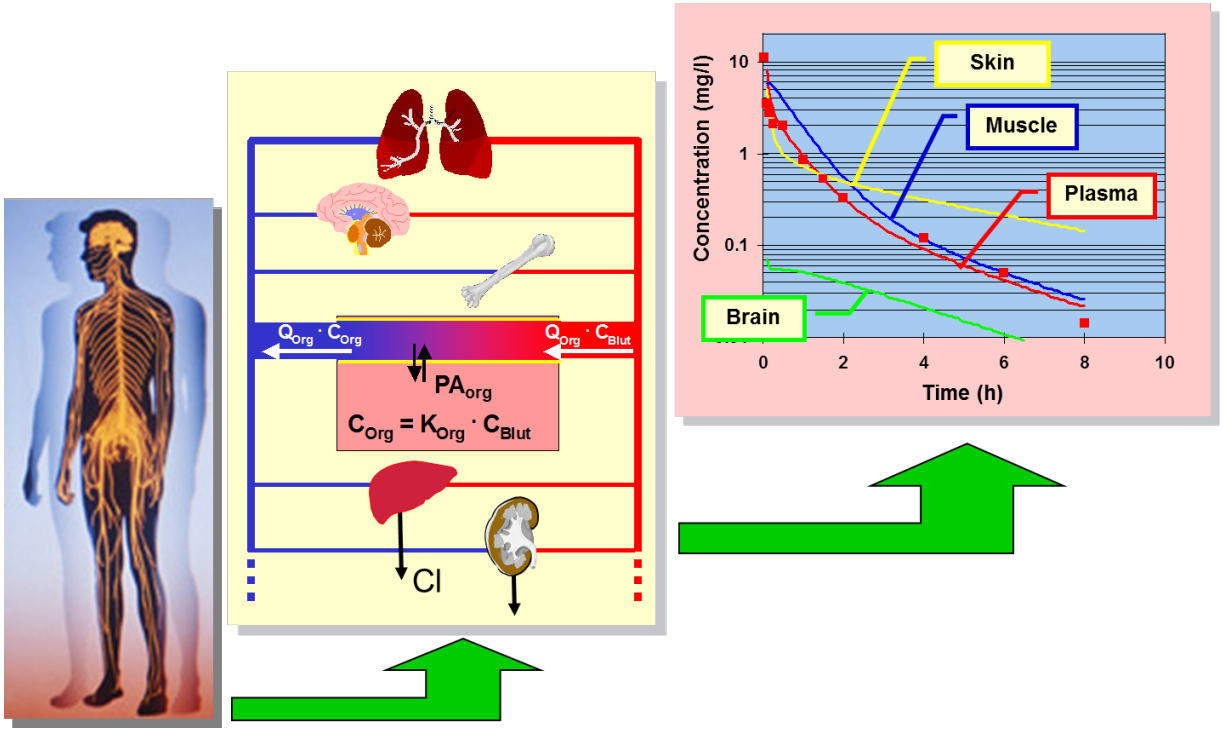
Tobias Kanacher

18.May.2014 in Stuttgart

Definition of PBPK Modelling

Wikipedia:

Physiologically based pharmacokinetic (PBPK) modeling is a mathematical modeling technique for predicting the absorption, distribution, metabolism and excretion (ADME) of synthetic or natural chemical substances in humans and other animal species



Early PBPK modelling

The general idea was introduced as early as 1924: *H. W. Haggard. The Absorption, Distribution and Elimination of Ethyl Ether. The Journal of Biological Chemistry. 59. 753-770. 1924.*

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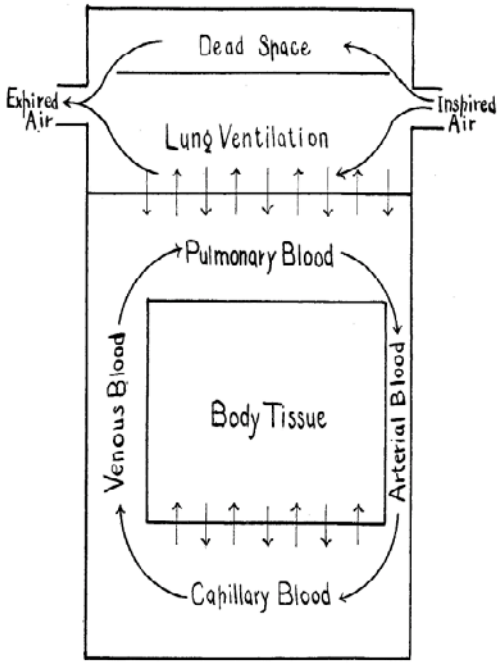

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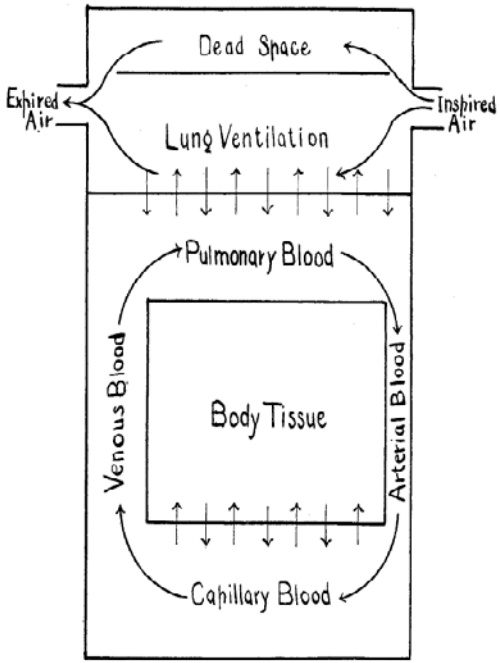

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(1) $x + x\,(1 - x)$ or $2x - x^2$

(2) $x + x\,(1 - x) + x\,[1 - (x + x)\,(1 - x)]$ or $3x - 3x^2 + x^3$

(4) The weight of ether absorbed in 1 minute $= \frac{LCBK}{BK + L}$

(3) $Ac = \frac{LCK}{BK + L}$

(5) The amount of ether exhaled from the lungs in 1 minute $= \frac{LCK}{BK + L}$

(6) Grams of ether absorbed during first round of circulation $= \frac{LCGK}{BK + L}$

(7) Grams of ether brought back to the lungs during second round of circulation $= \frac{LCGK}{BK + K} \times \frac{G}{W}$

(8) Grams of ether absorbed during second round of circulation $= \frac{LCG}{B} + \frac{LCG^2K}{W\,(BK + L)} \times \frac{BK}{BK + L}$

(9) Ether content of alveolar air in grams per liter $= \frac{Ac}{K}$

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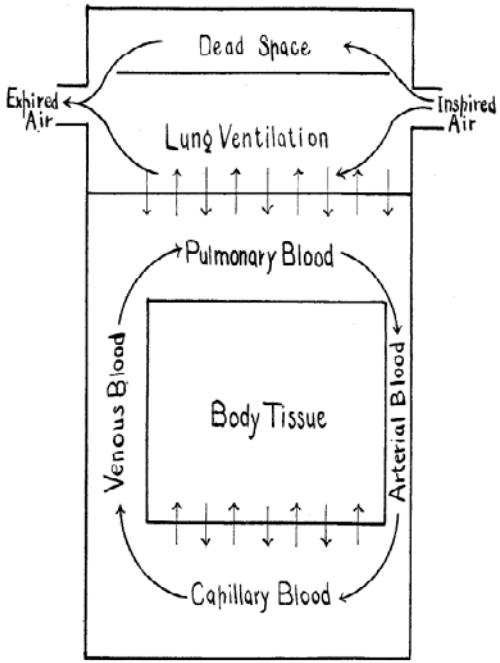

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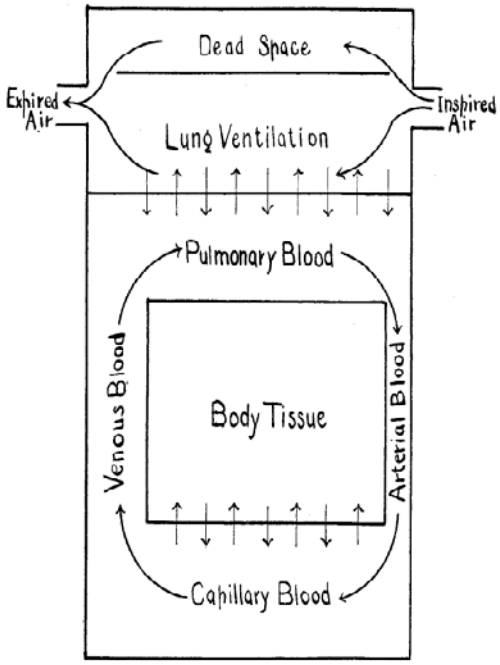

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create/ sketch a model

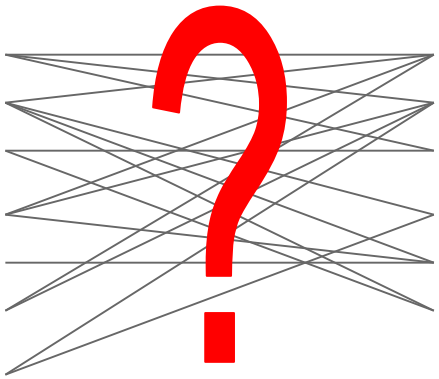
use model for calculation/ predictions

validate model

Correlating *in vitro* data with *in vivo* PK

Physico-chemical-/ *in vitro* properties

- octanol/water PC
- membrane affinity
- HSA affinity
- solubility
- Caco2-permeability
- Polar Surface Area
- microsomal metabolic rate
- ...



Pharmacokinetic-/ADME- *in vivo* properties

- fraction dose absorbed
- bioavailability
- organ/plasma PC
- clearance
- C_{max}, T_{max}
- free serum concentration
- respiratory uptake ratio
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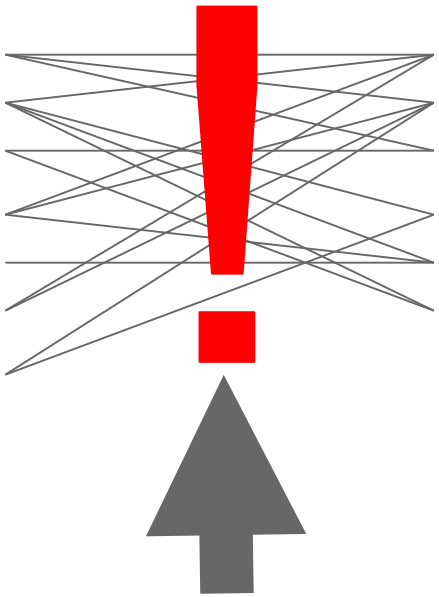

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PHYSIOLOGY OF THE ORGANISM

organ volume and composition, blood flow rates, pH, effective accessible surface area, gastric emptying and intestinal transit time, feeding status, gender, age, ...

Parameters of a PBPK Model

Physiological Parameters

- Organ volumes
- Blood flow rates
- Tissue composition
- Expression levels
- Turnover rates
- …

available in literature
→is contained in PK-Sim

Substance-Specific Parameters

Passive

- Partition coefficients
- Permeability coefficients
- …

Predicted from physico -chem. surrogate parameters
→ done by PK-Sim

Active

- Rate constants (V_{max}, K_m) for elimination and active transport processes

determined *in vitro* or fitted from *in vivo data*

PBPK Challenge & Opportunity

How to predict pharmacokinetics in humans and/or other species?

PBPK Challenge & Opportunity

Set up whole-body physiological pharmacokinetic model integrating all available data as a quantitative representation of biological processes driving pharmacokinetics

- Pharmacokinetic-/ADME- *in vivo* properties
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- Physiological properties

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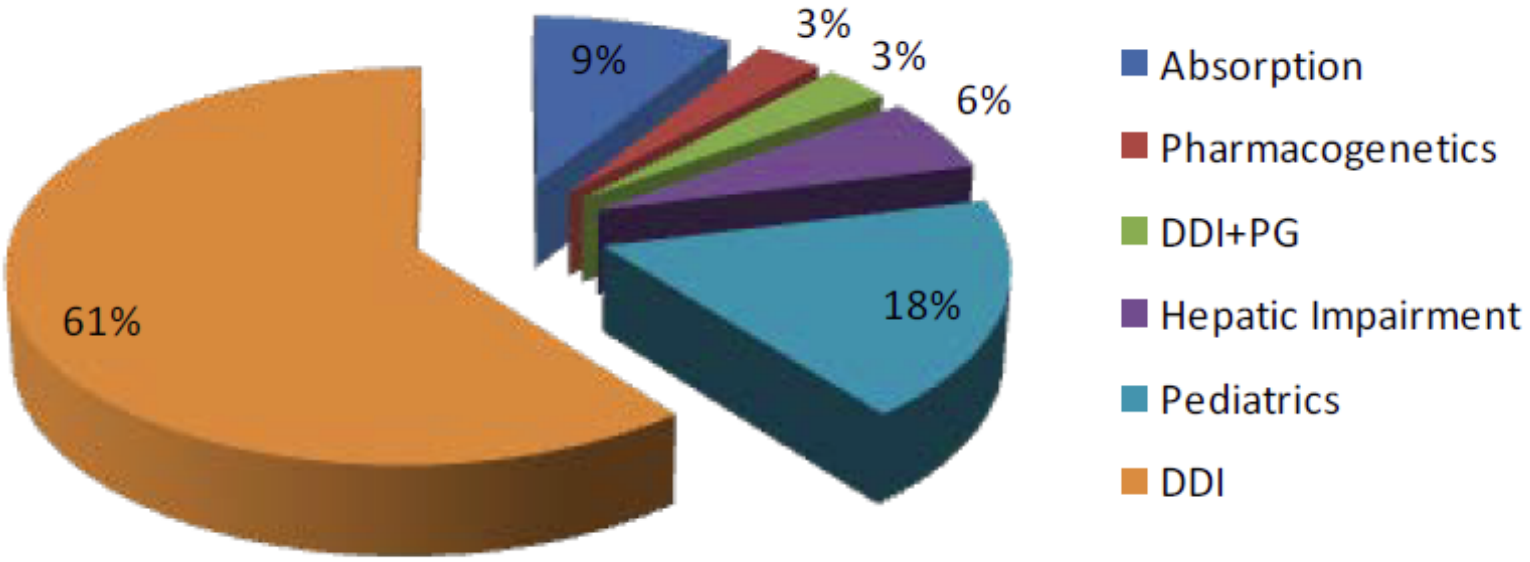
Position of Regulatory Agencies (FDA)

‘Physiologically based pharmacokinetic (PBPK) modeling and simulation is a tool that can help predict the pharmacokinetics of drugs in humans and evaluate the effects of intrinsic (e.g., organ dysfunction, age, genetics) and extrinsic (e.g., drug-drug interactions) factors, alone or in combinations, on drug exposure.

The use of this tool is increasing at all stages of the drug development process.’

Zhao P *et al.*, Clin Pharmacol Ther. 2011

Regulatory Submissions with PBPK Data (provided by FDA)

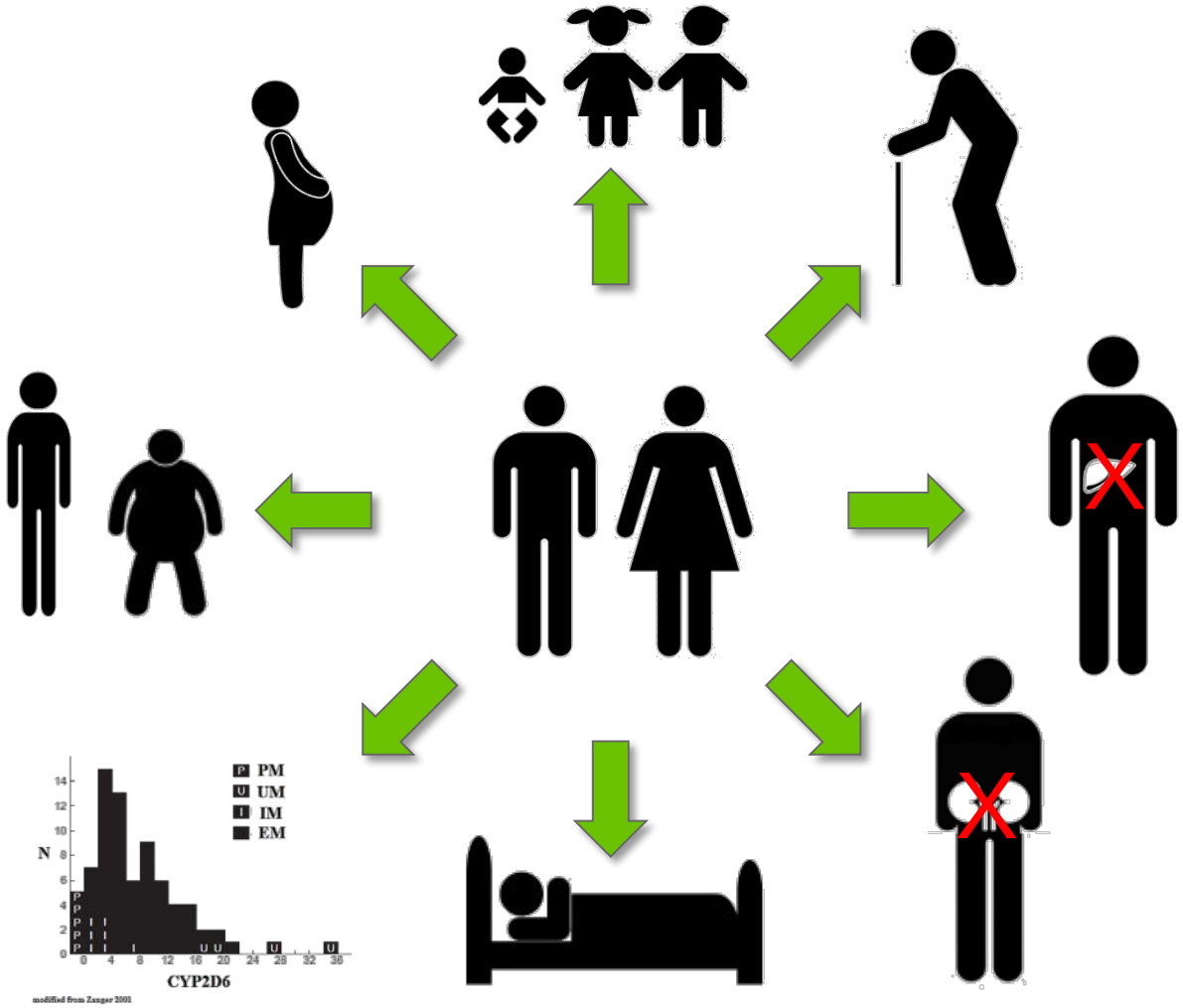


Areas of application in the 33 PBPK submissions in IND/NDA received by FDA's Office of Clinical Pharmacology from 2008 to 2012

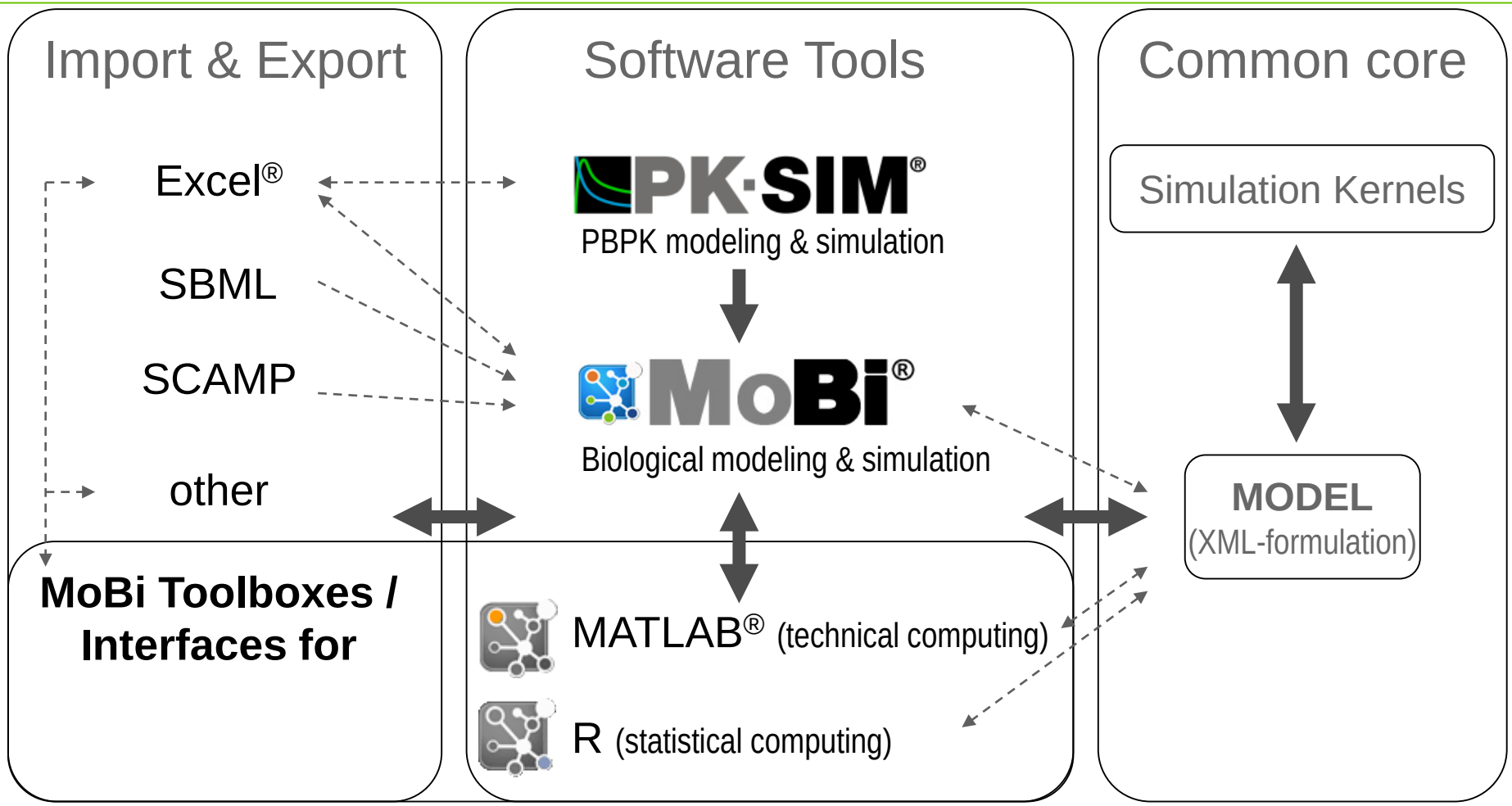
Huang, Abernethy, Wang, Zhao, Zineh, J Pharm Sci (submitted)

Slide from A. Edginton, ACOP 2013

Main Area of Application: Special Populations



The BTS Software Platform



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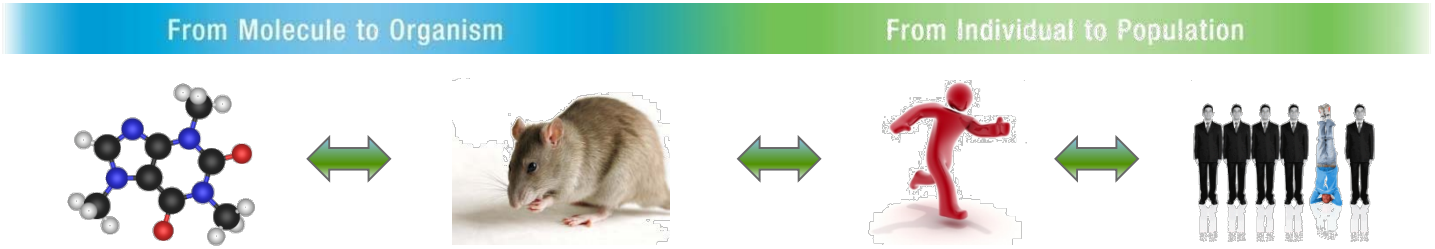
BTS Systems Biology Software Suite: Multiscale Mechanistic Modeling



PK-Sim®

MoBi® Toolbox for MATLAB®

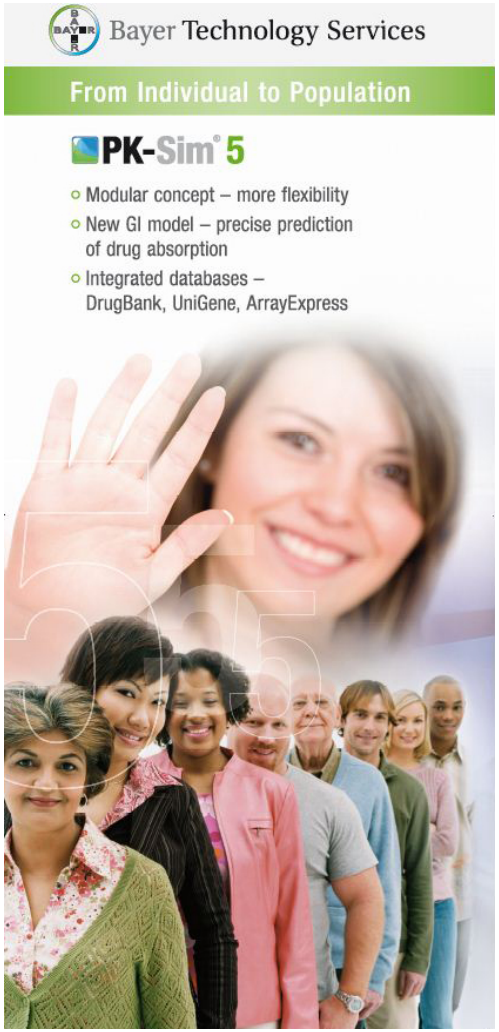
MoBi®

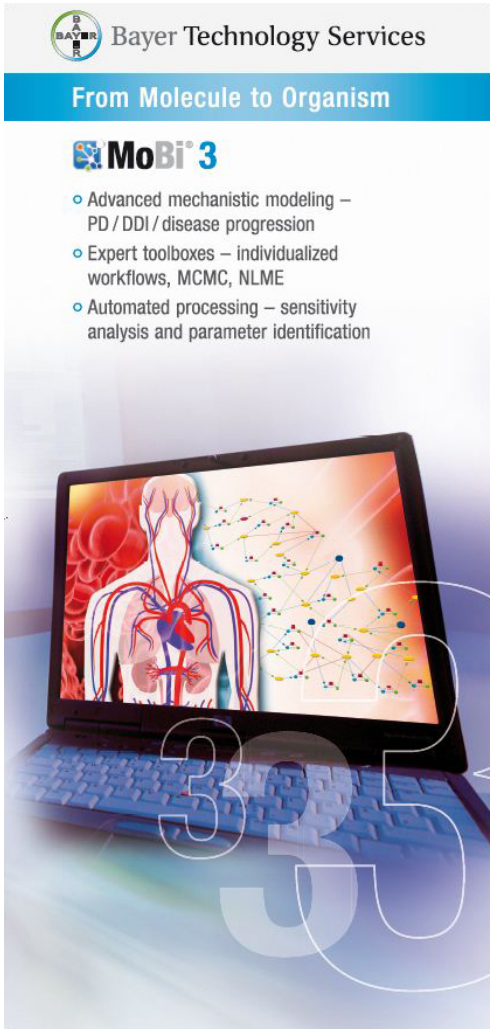
MoBi® Toolbox for R

PK-Sim for academic Users

- **It is for free!**
- The software will be used only for academic purposes without any commercial background
- If PK-Sim is used in research or data analysis, it consequently has to be cited in the resulting publications
- You will allow Bayer Technology Services GmbH (BTS) to mention your Group/Department/University together with its logo on BTS homepages and other marketing material
- Inquire at info@systems-biology.com

New Software Platform with PK-Sim 5 and MoBi 3





Shortlist new Features:

Complete Redesign; new modular Building Block Concept

Full integration and compatibility between PK-Sim® and MoBi®

Better target concentration accuracy: PK-Sim Express®

New compartmental gastro-intestinal transit model

Full transparency and improved user convenience: History and Rollback function

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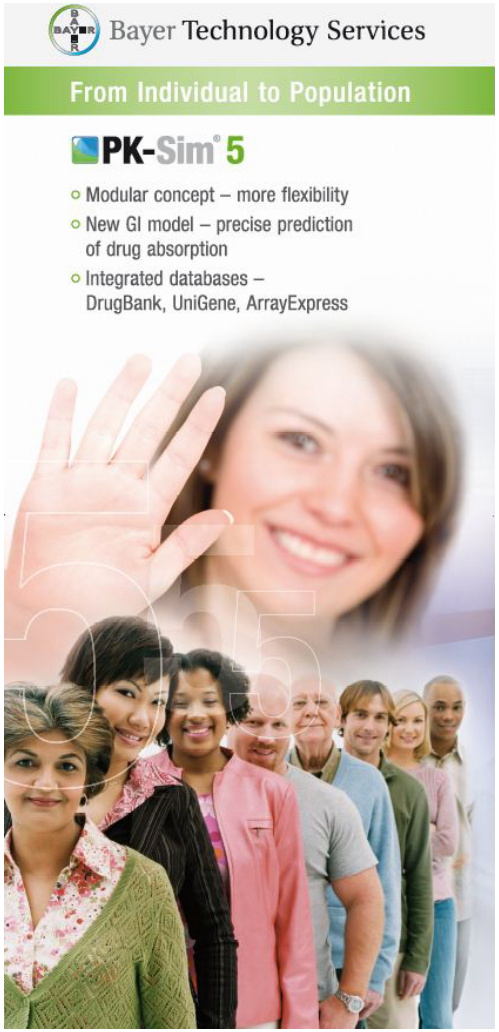

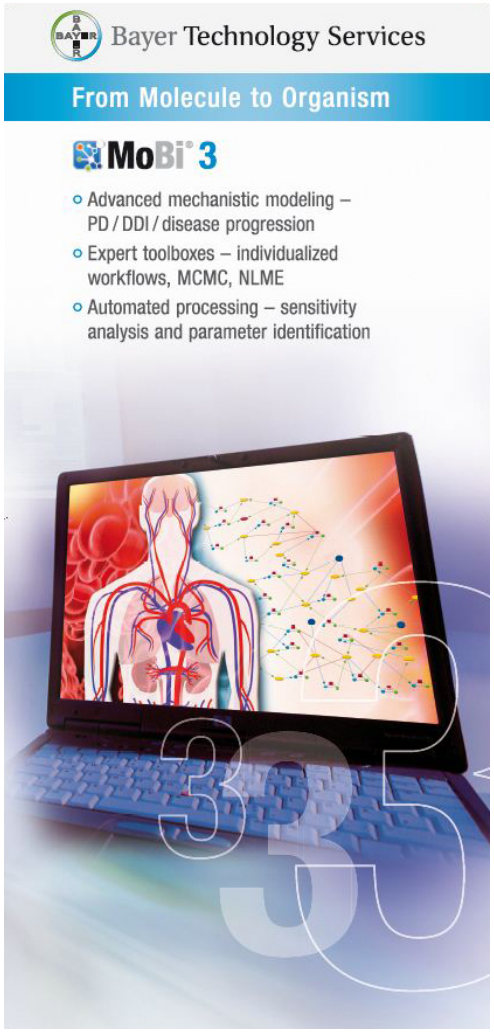

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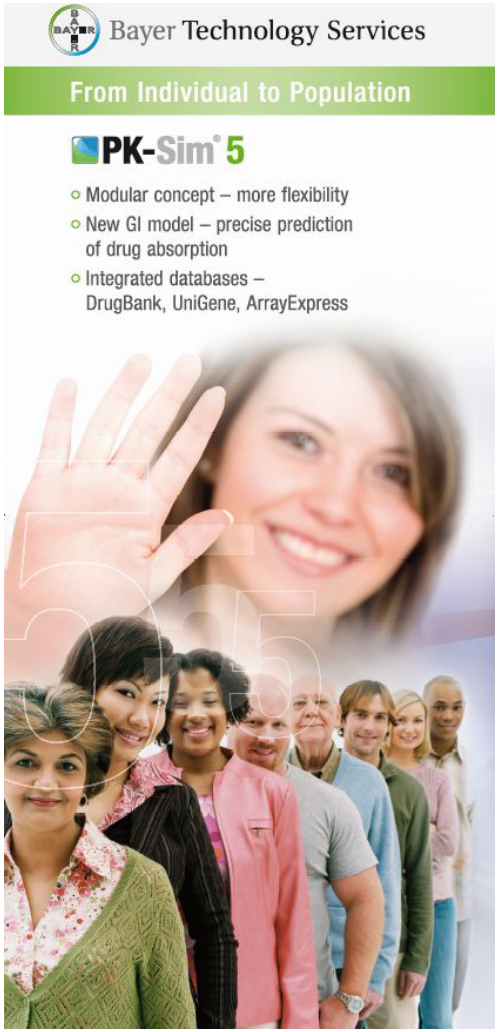

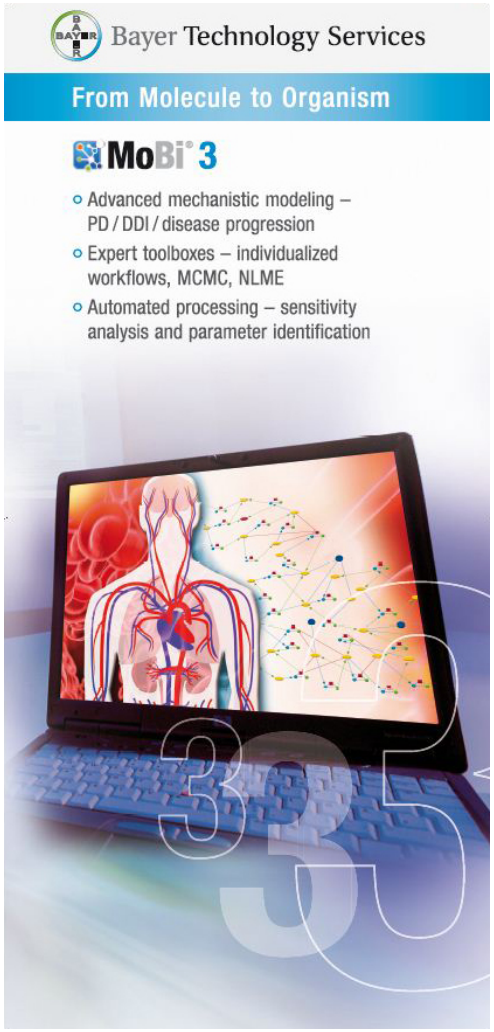

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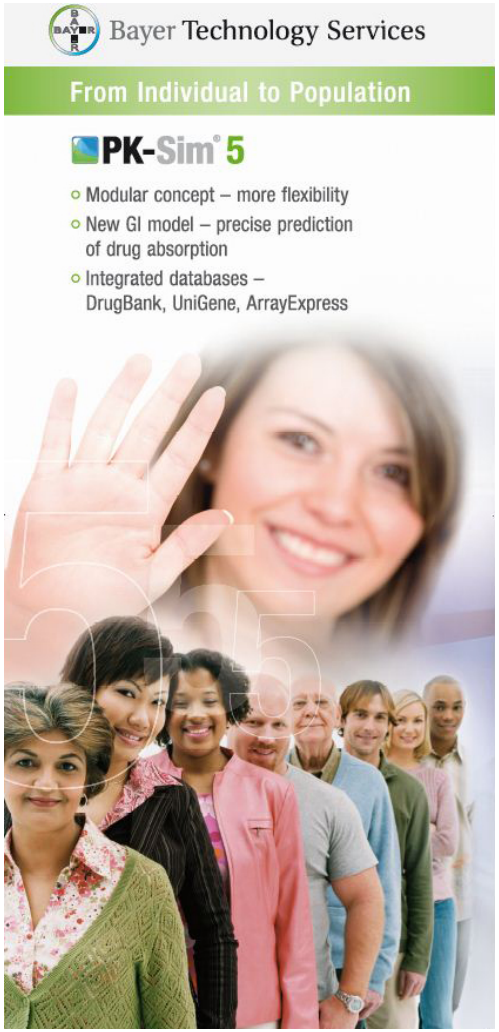

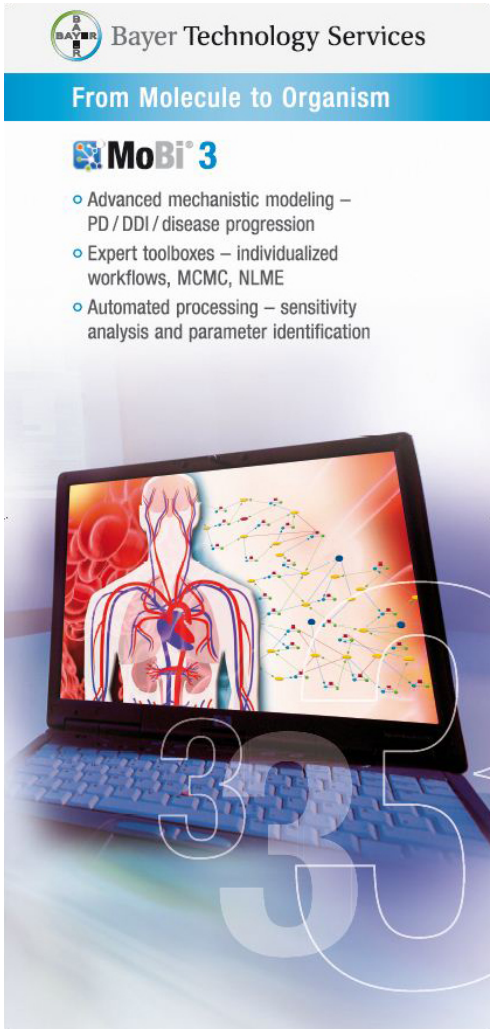

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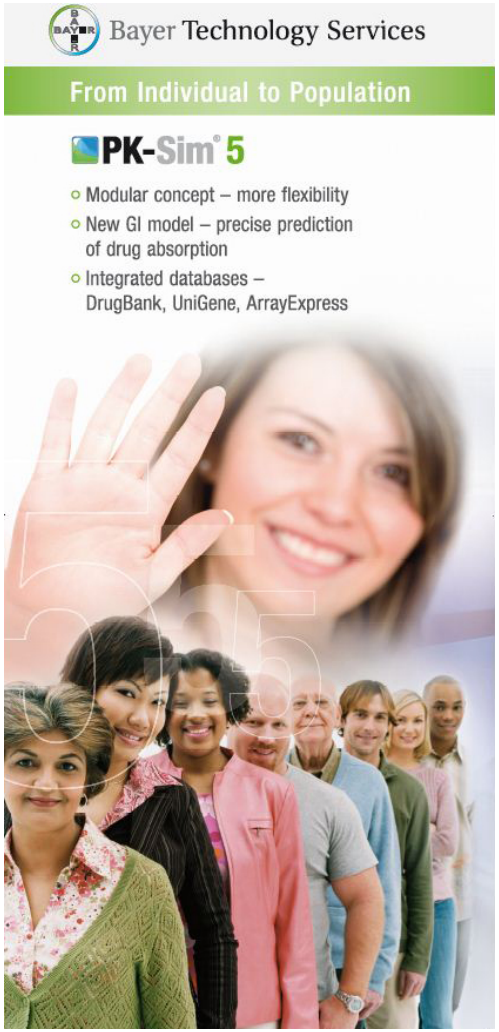

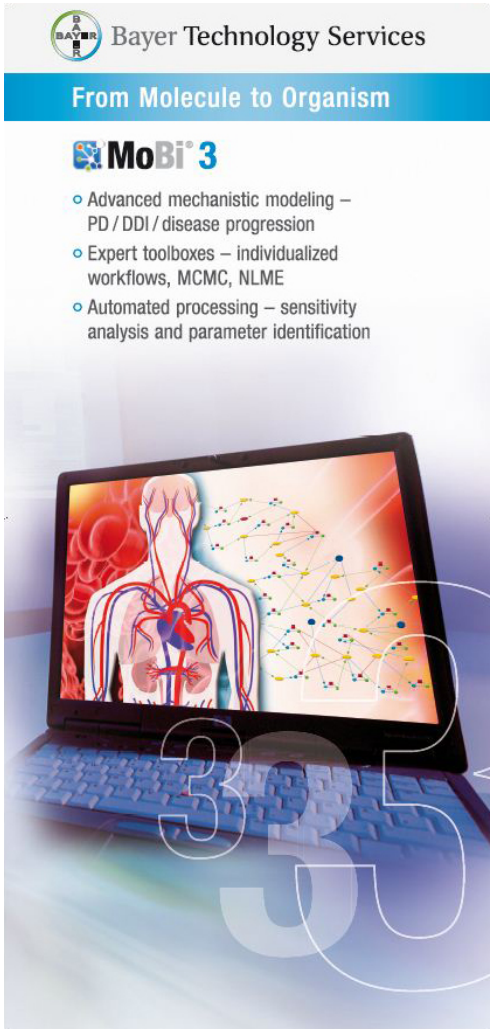

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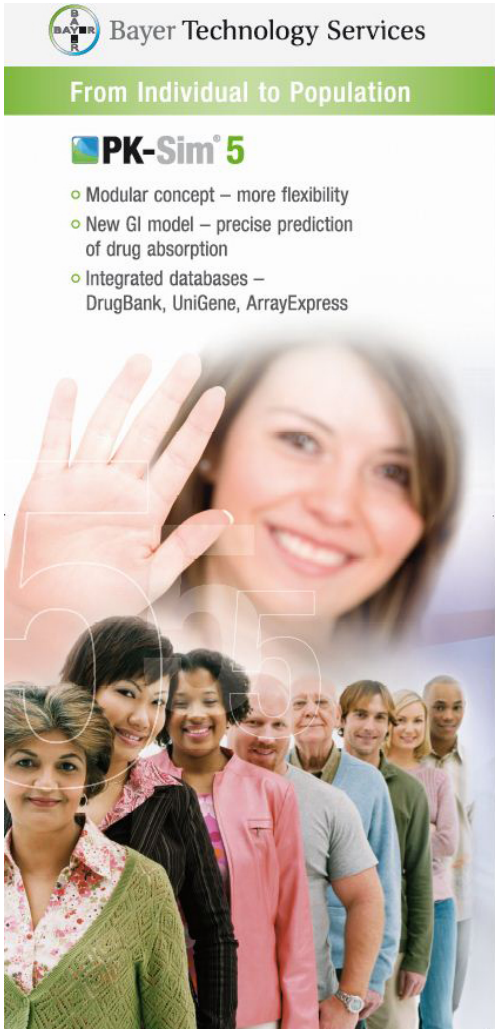

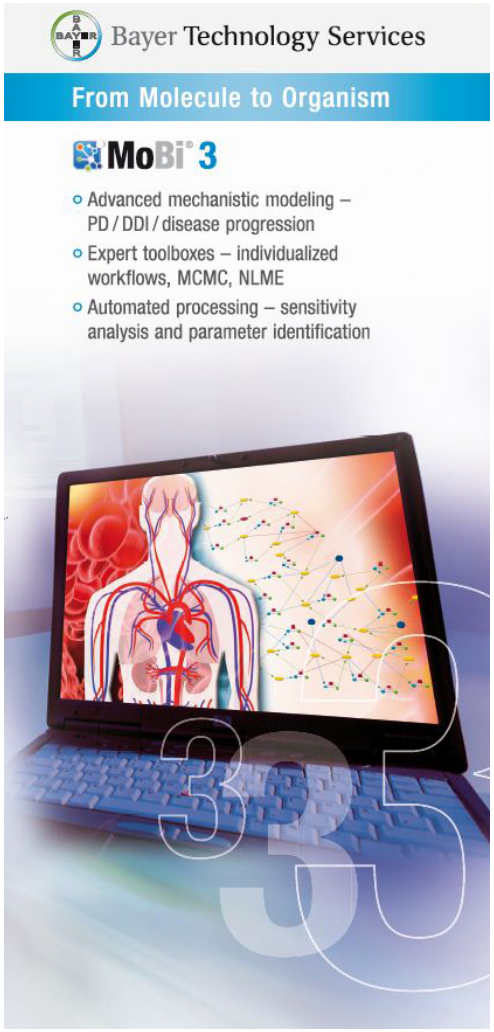

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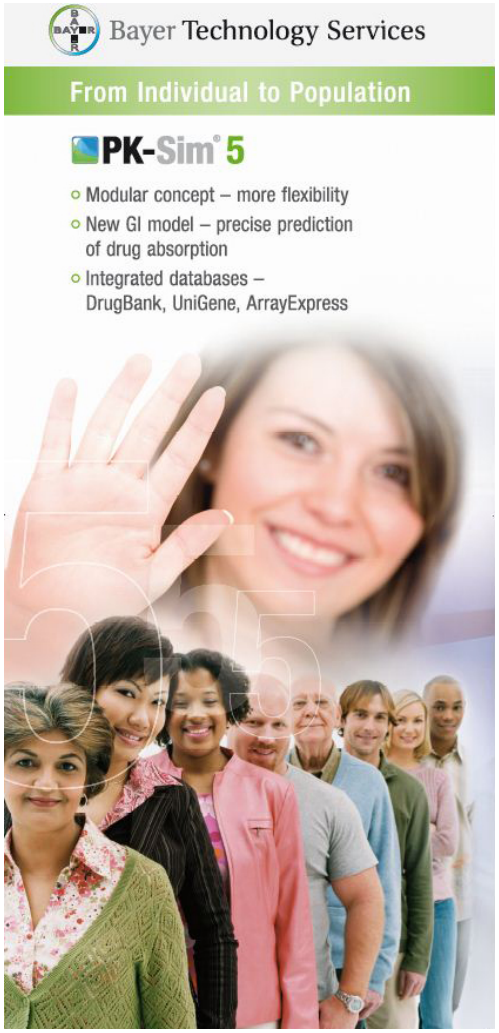

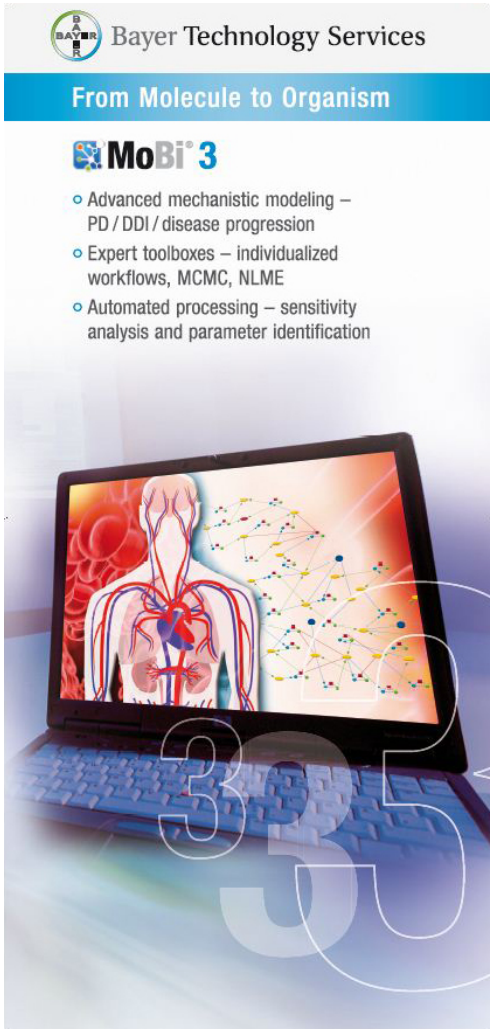

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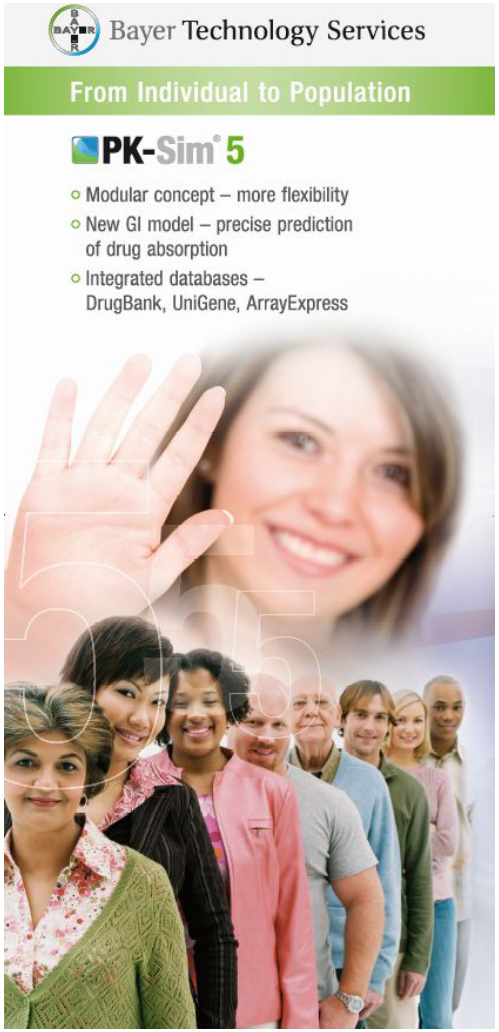

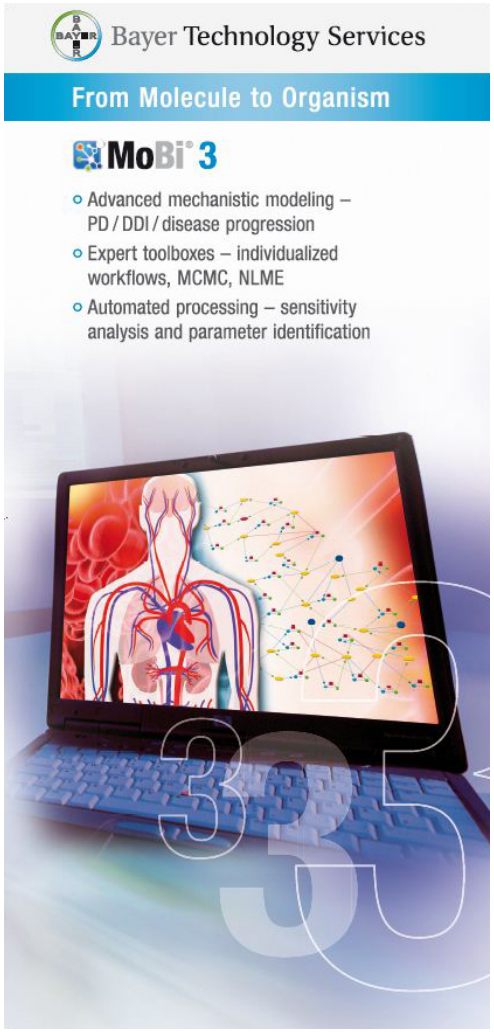

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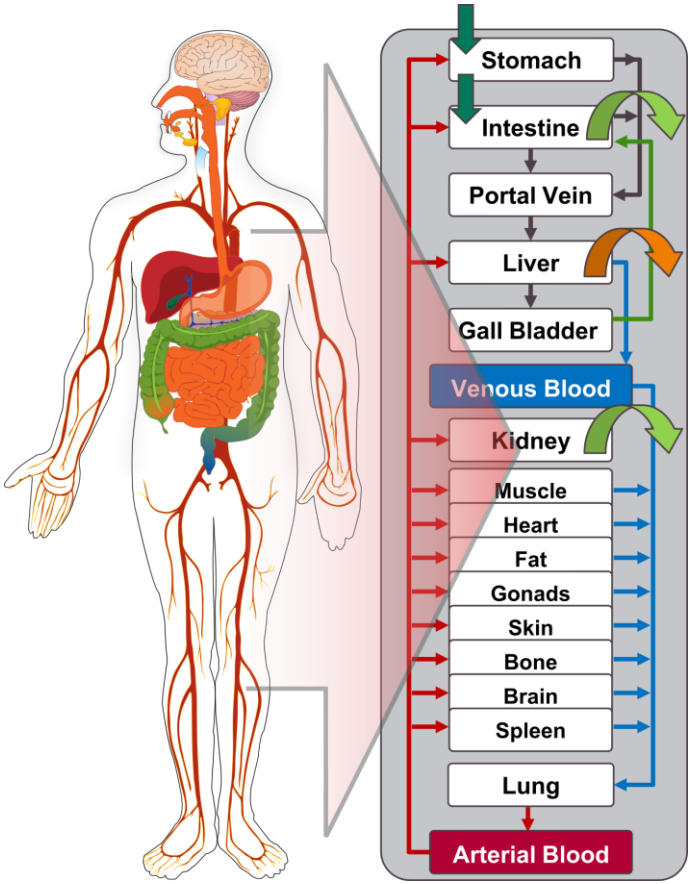
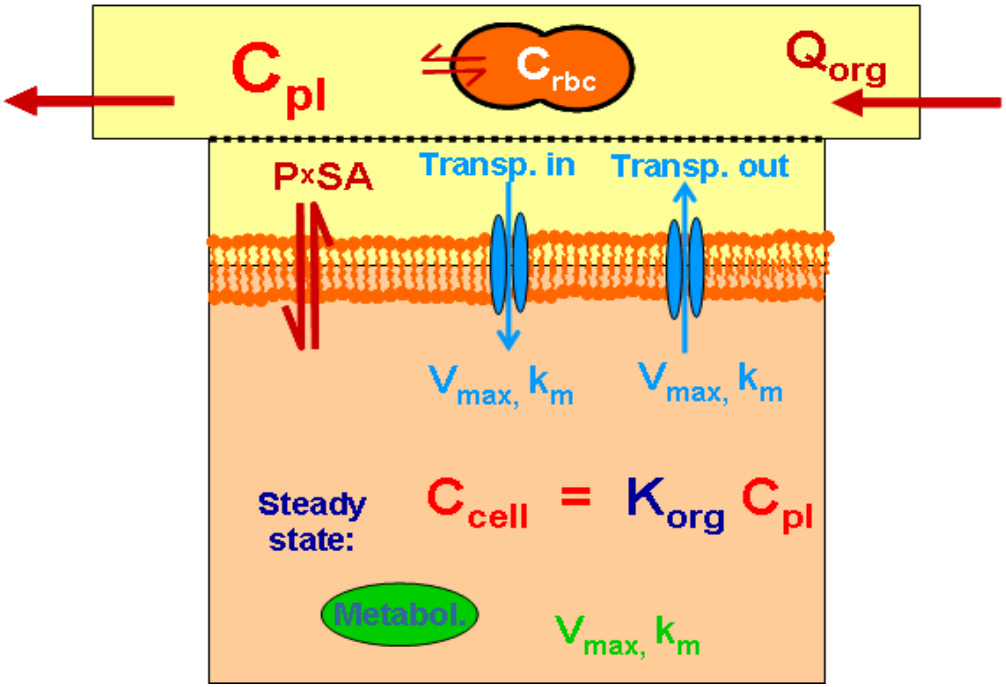
PK-Sim Model structure

Model structure

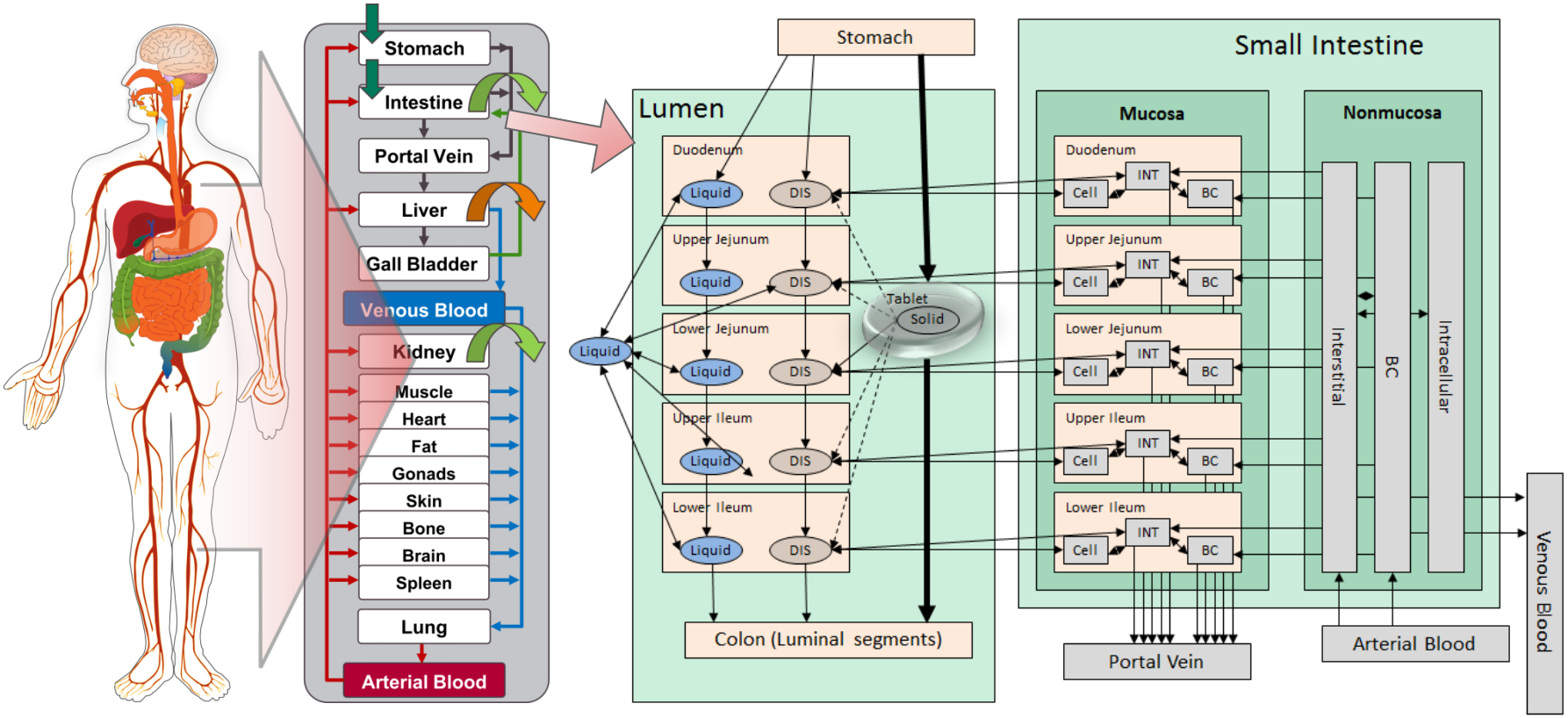


Organ substructure



Basic PBPK model structure and organ substructure implemented in PK-Sim®

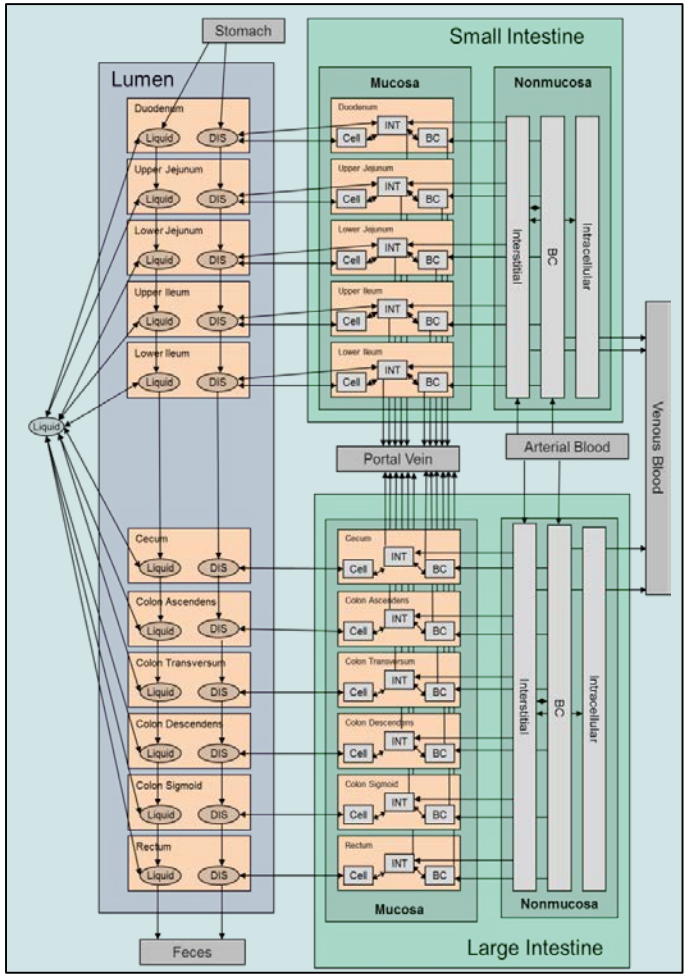
New Fully Compartmental Gastro-Intestinal Model



Basic PBPK model structure implemented in PK-Sim® and detailed model structure of the gastrointestinal tract. For better visualization, the large intestine is not shown.

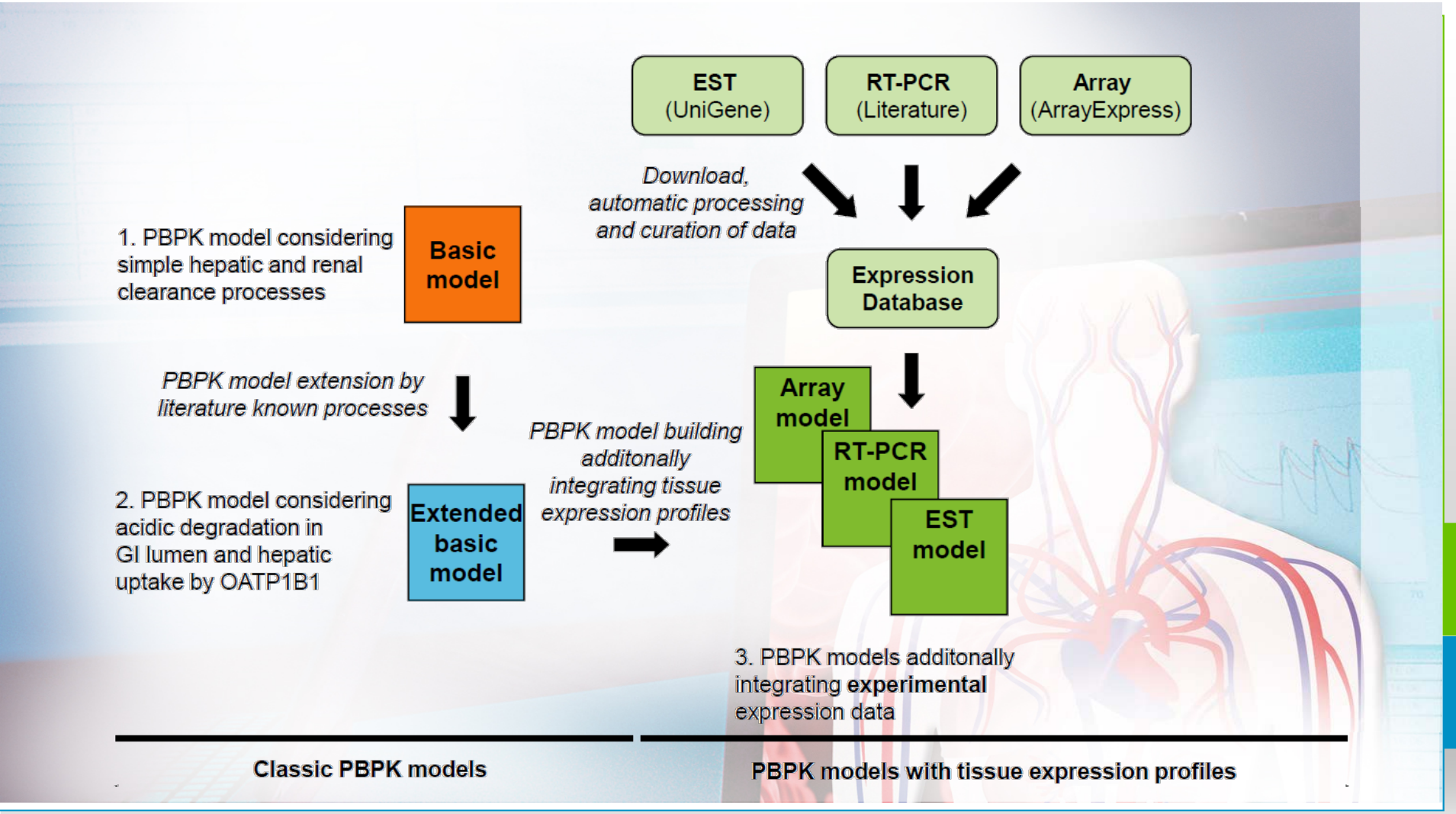
A New Compartmental Gastro-Intestinal Transit Model

- 12 compartments representing the lumen of the GI tract from stomach to rectum
- Varying properties:
  - Dimensions
  - pH values
  - absorptive surface area
  - transit times
- 11 compartments representing the intestinal mucosa which is (subdivided into enterocytes, interstitial and vascular space)
- Explicit representation of intestinal mucosa allows to account for
  - CYP distribution
  - transporter distribution



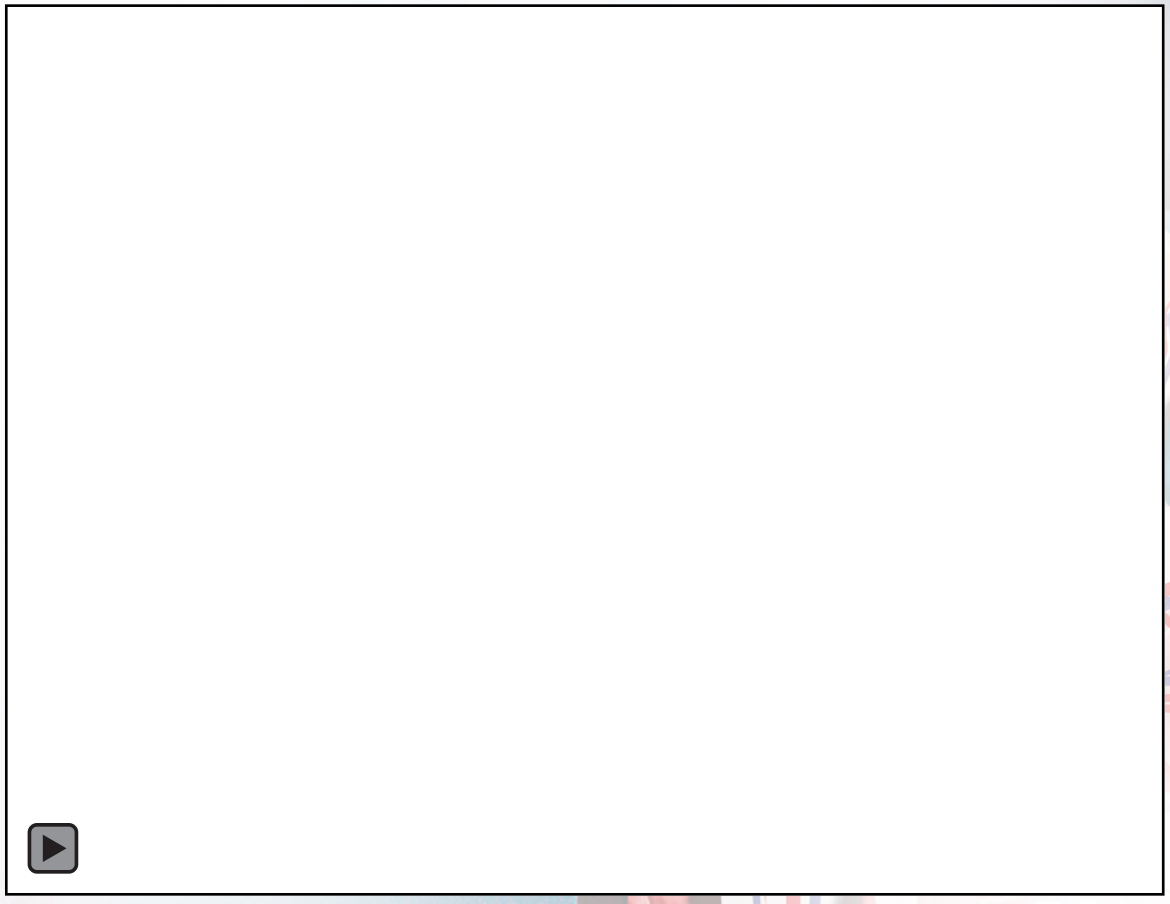
Thelen 2011/2

Integration of Expression Data



History and Rollback function

We judge it a fundamental neccessity with regard to transparency that for PBPK models all parameters are visible and that all calculations can be independently reproduced.

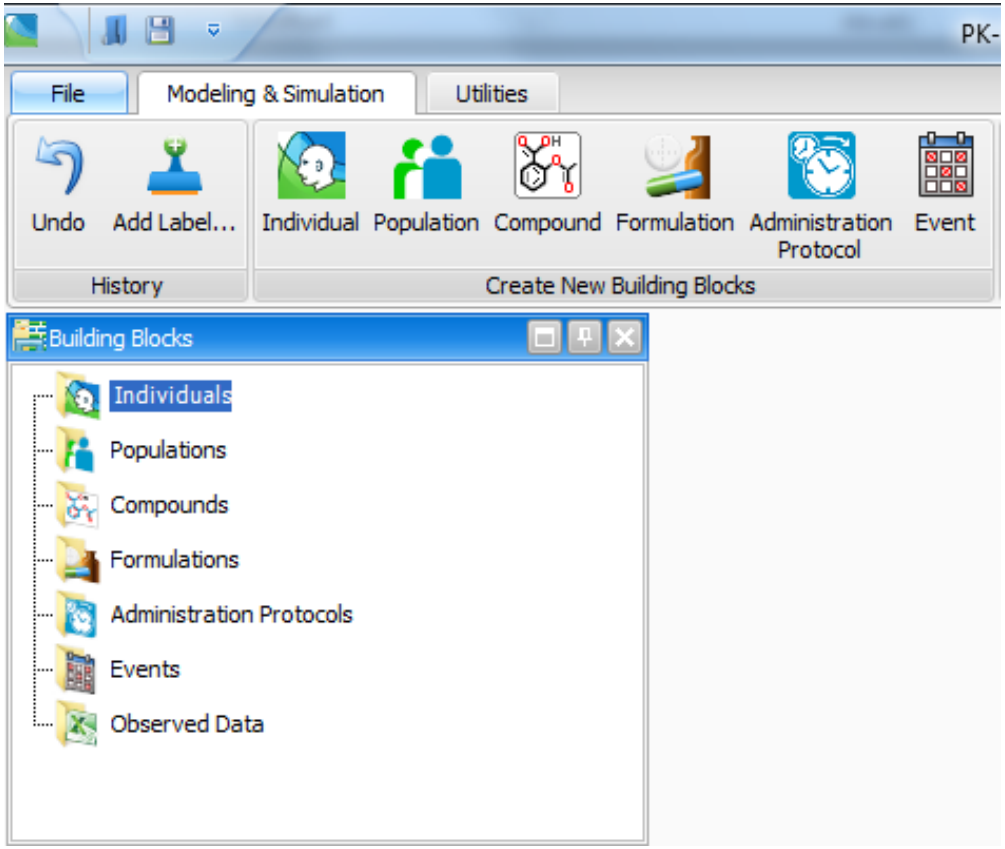


The PK-Sim Building Block Concept

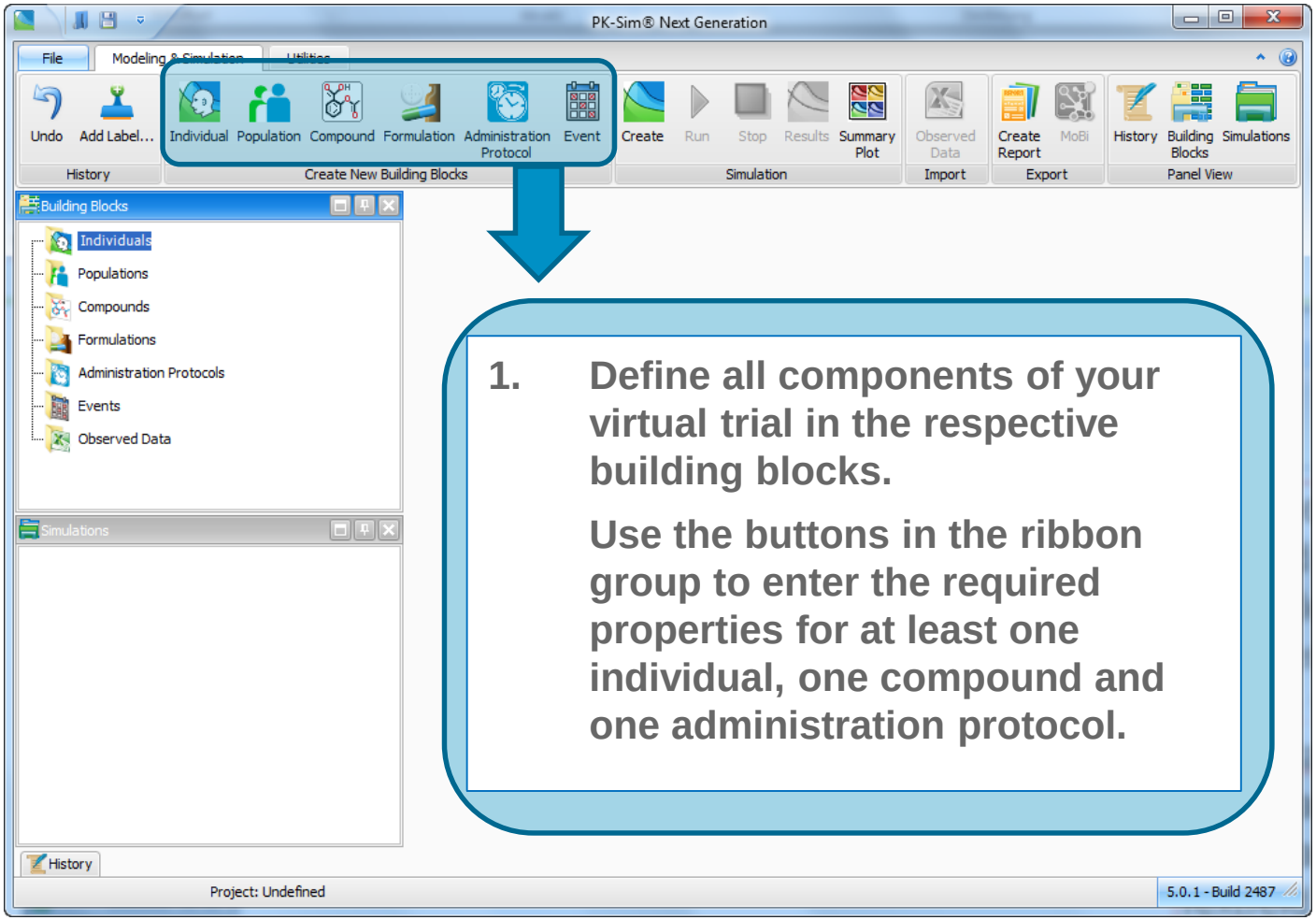
Independent building blocks for:

- **Individual**
- **Population**
- **Compound**
- **Formulation**
- **Administration Protocol**
- **Event**

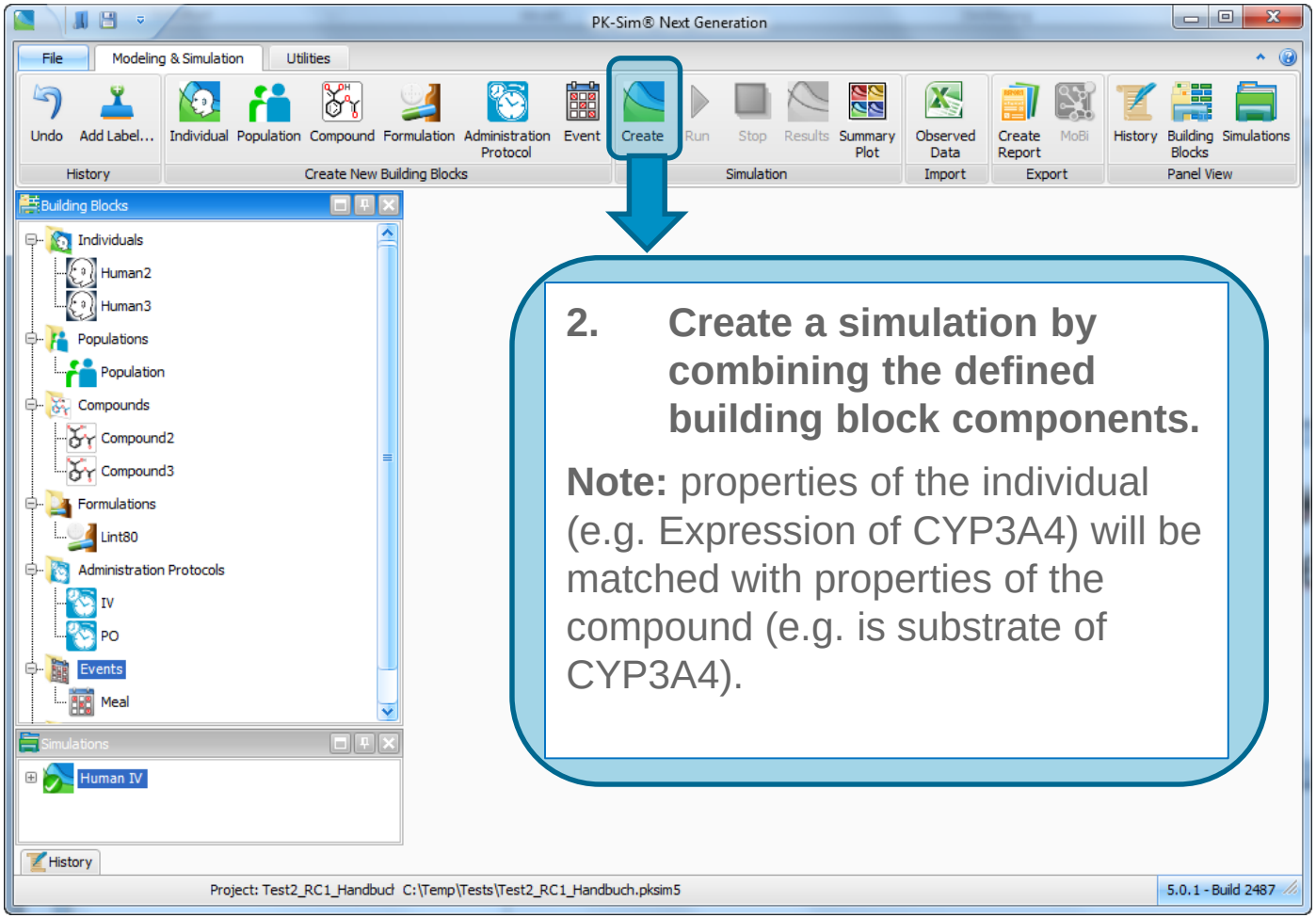
Active Processes such as renal and hepatic clearance, protein binding etc. are allocated when a simulation is created from the corresponding building blocks. Building blocks can be saved to create an evolving repository.



PK-Sim: Workflow – Quick Guide 1



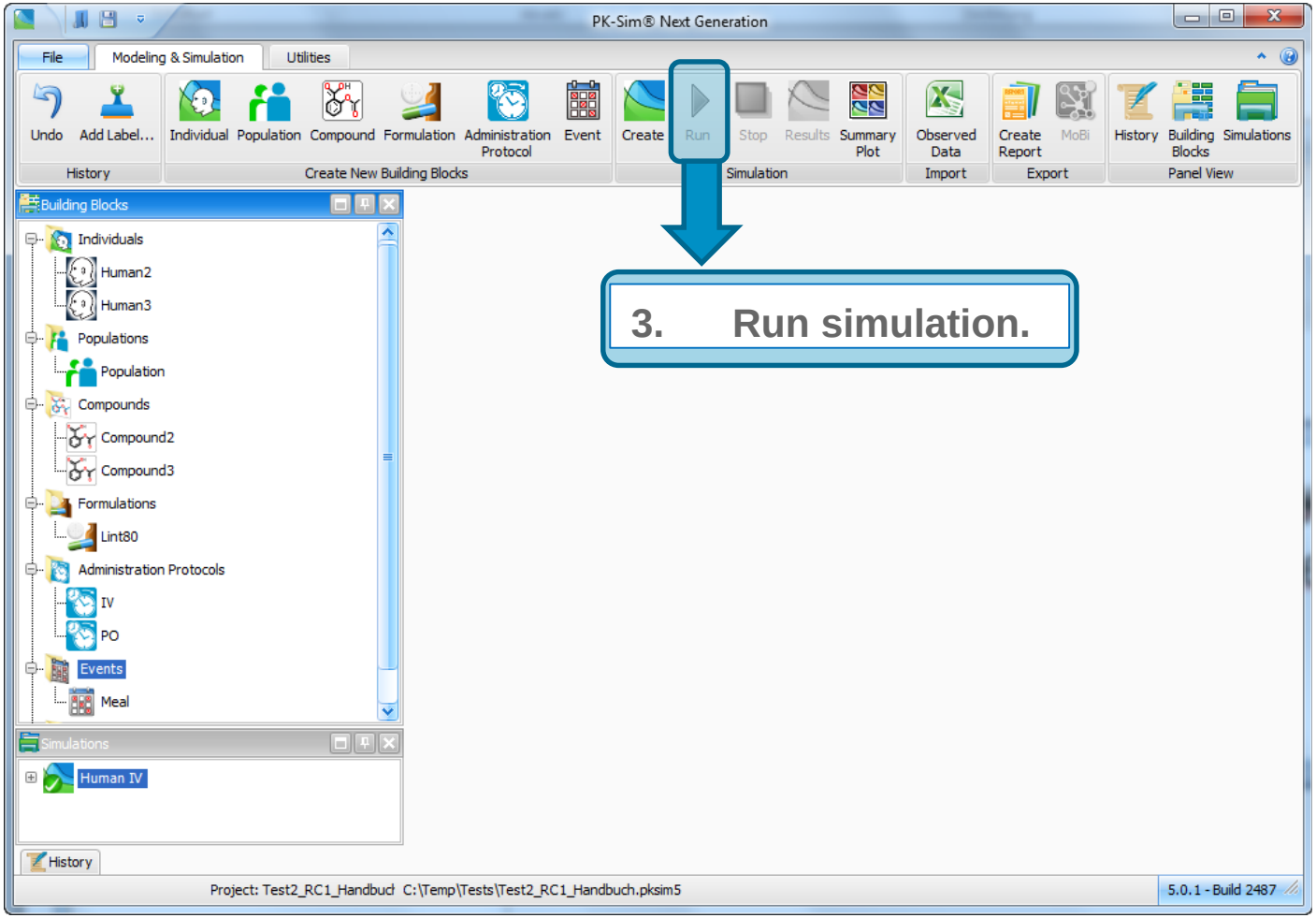
PK-Sim: Workflow – Quick Guide 2



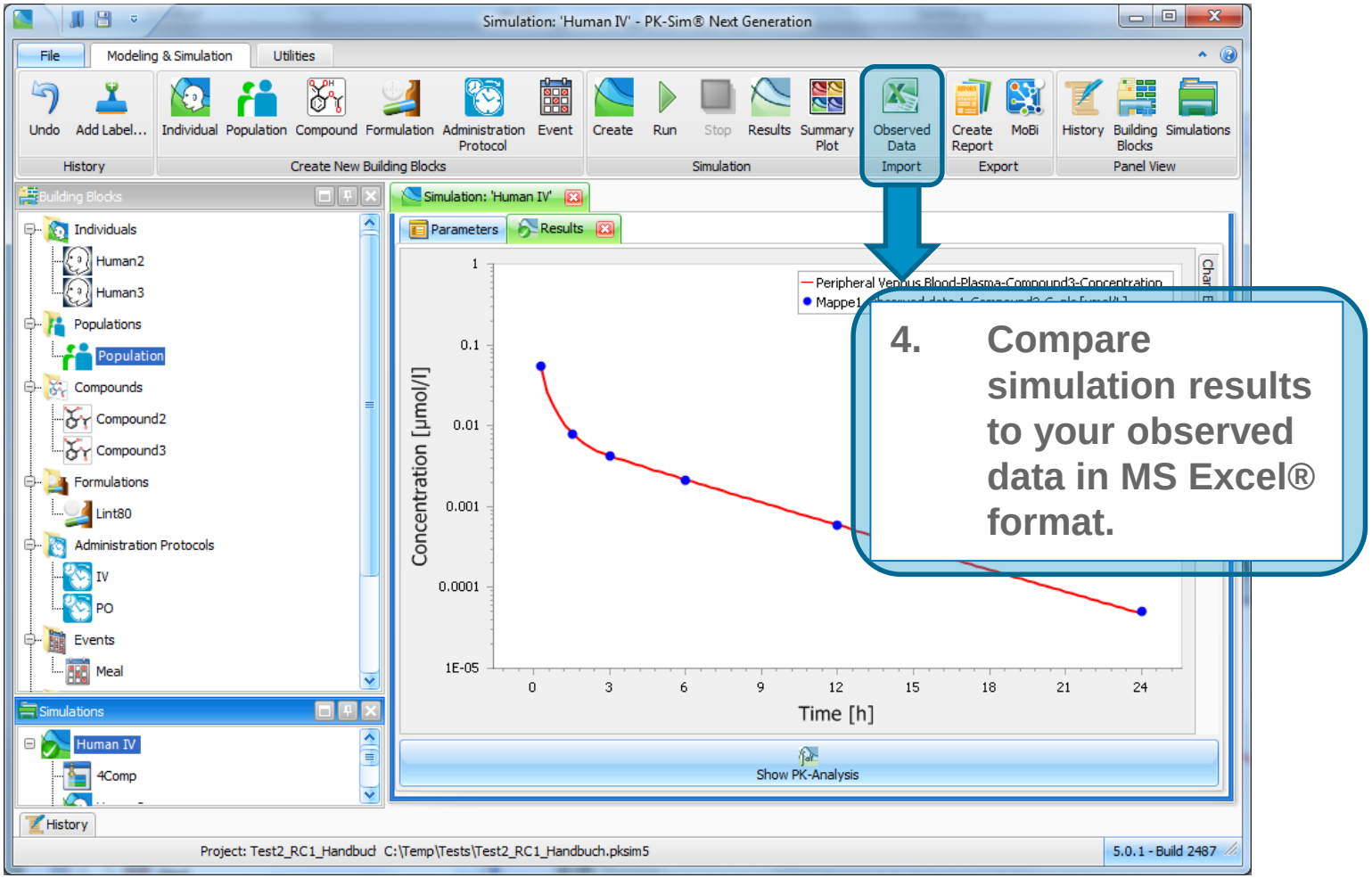
2. Create a simulation by combining the defined building block components.

Note: properties of the individual (e.g. Expression of CYP3A4) will be matched with properties of the compound (e.g. is substrate of CYP3A4).

PK-Sim: Workflow – Quick Guide 3

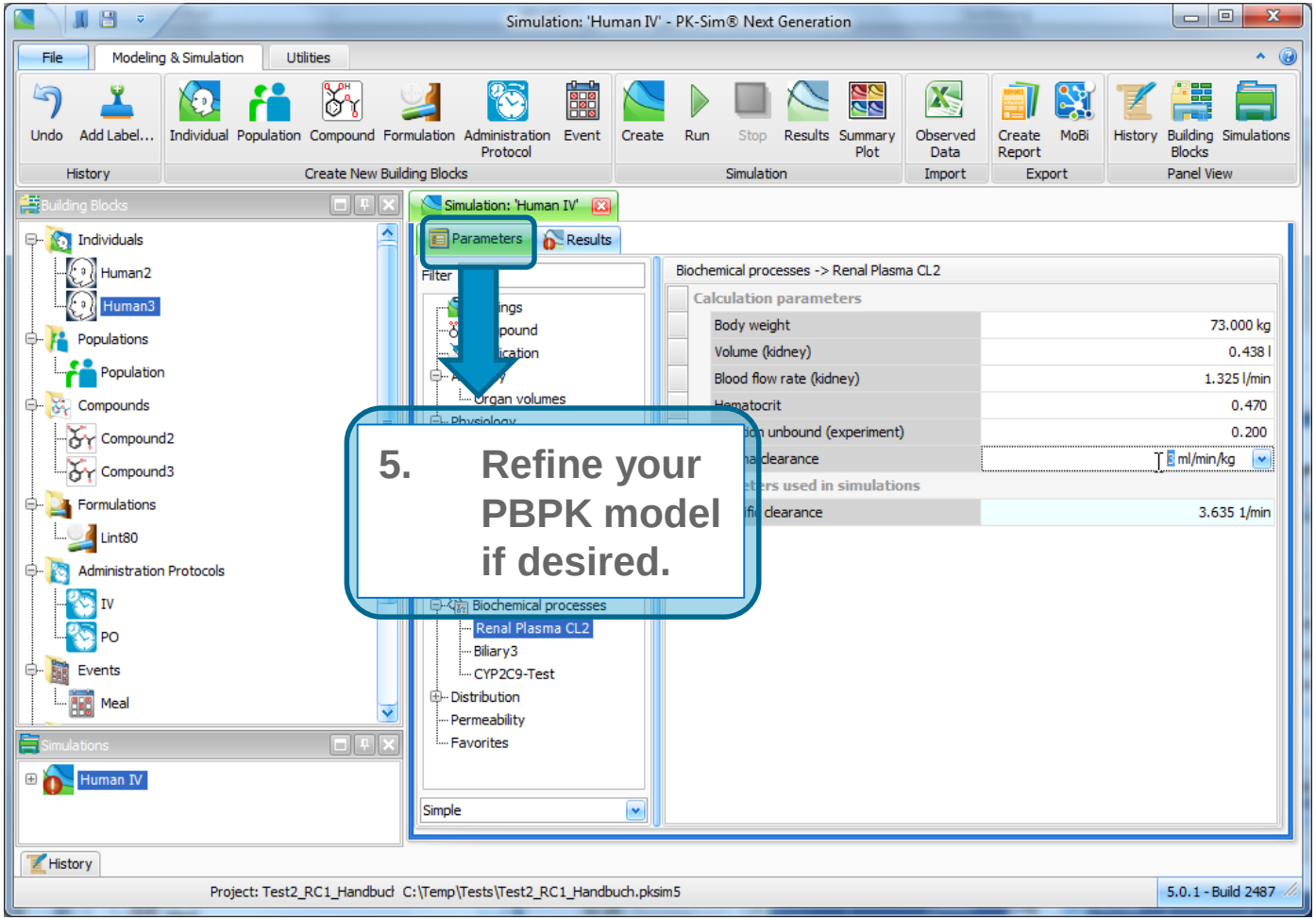


PK-Sim: Workflow – Quick Guide 4

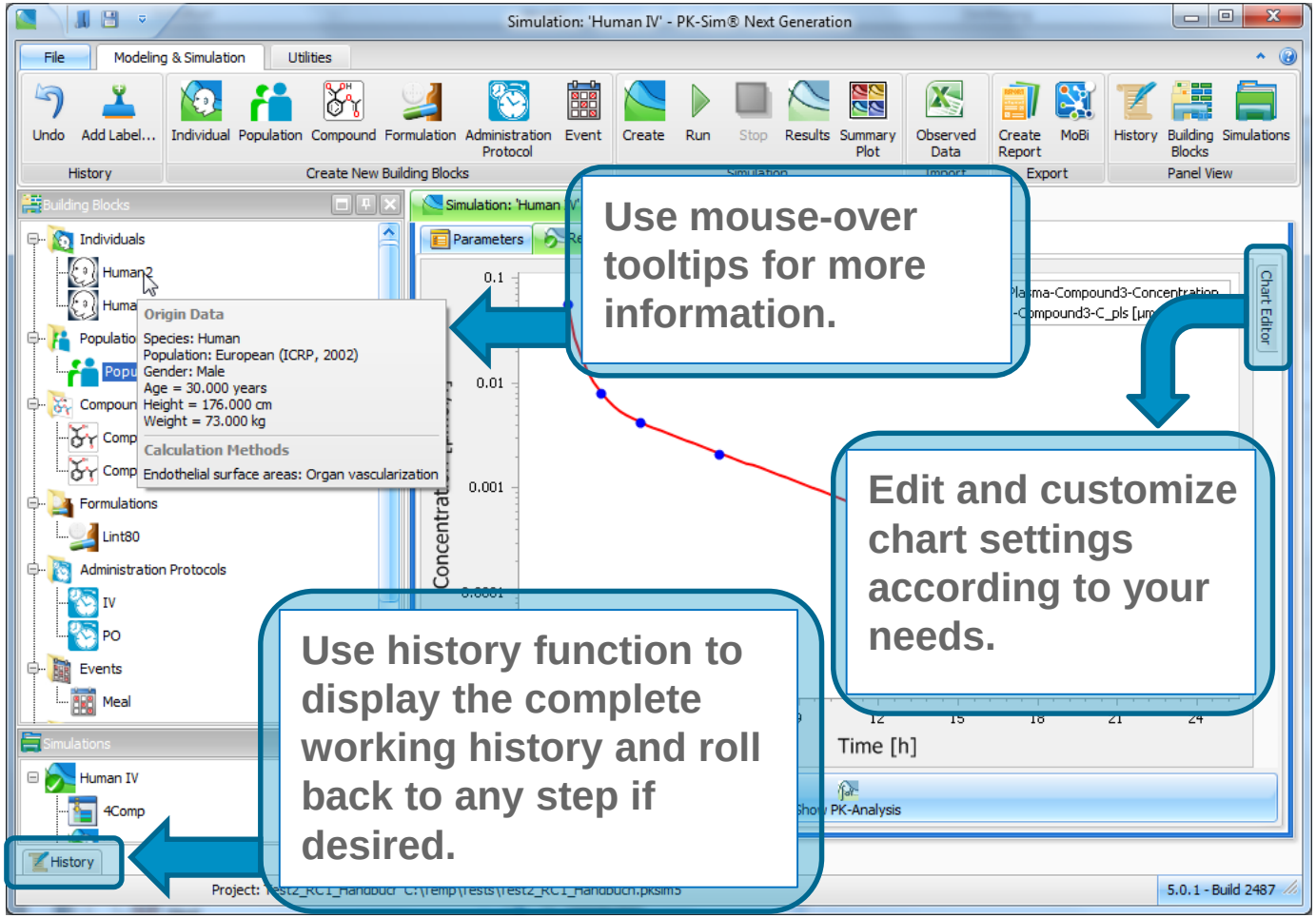


4. Compare simulation results to your observed data in MS Excel® format.

PK-Sim: Workflow – Quick Guide 5



PK-Sim: Workflow – Quick Guide 6



Demo: Insertion Of An Active Transport

Objectives:

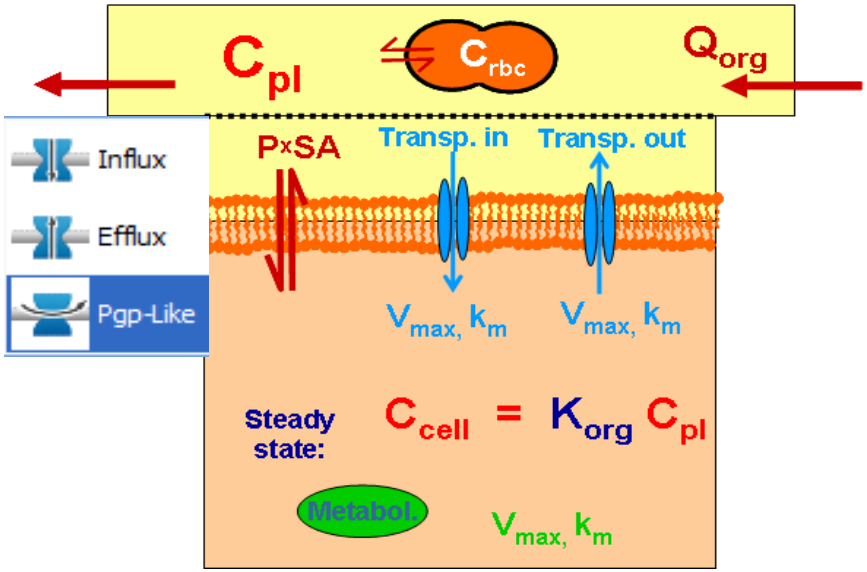
1. Input and adjustment of clearance parameters
2. Simulation of organ concentrations
3. Hypotheses testing
4. Clone a species
5. Insert active transport mechanism

Background:

- Passive distribution rates into organs are determined by the permeability surface area products ($PxSA_{org}$ and $PxSA_{rbc}$). These PxSA-values are rate limiting if the blood flow rate to the organ is larger than PxSA, otherwise the model gives way to a blood flow limited scenario
- However, in addition to the passive distribution into organs active transport processes can play a significant role, in particular if the affected organ is involved in the elimination of the compound

PK-Sim®: Sub-structure of the PBPK Model

- Each organ is further divided into sub- compartments representing the cellular, interstitial, and vascular space (plasma and blood cells)
- The plasma and interstitial space are represented as two distinct compartments (four sub-compartments per organ)
- For each organ:
  - metabolizing pathways
  - different active transporter types (influx, efflux, Pgp-like)



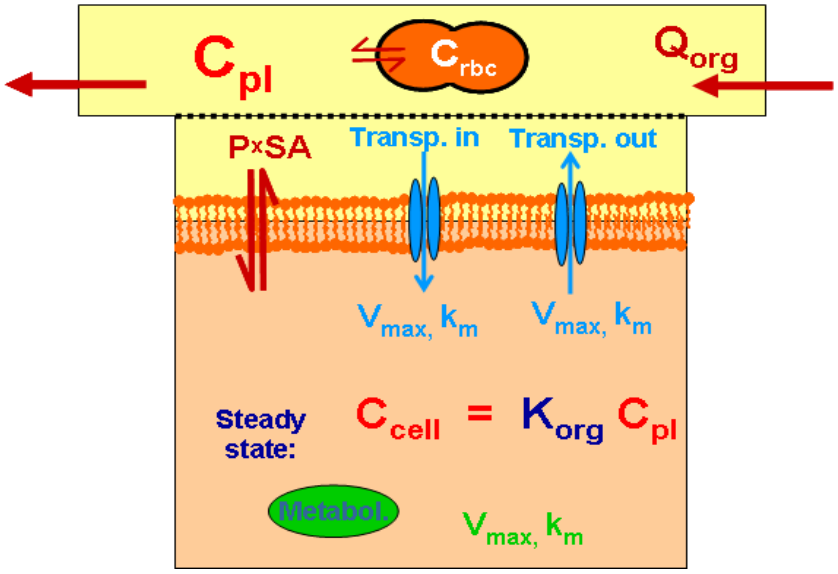
PK-Sim®: Sub-structure of the PBPK Model

Body-specific parameters:

- ⇨ Volumes (Blood Cells, Intracellular, Interstitial)
- ⇨ Flow Rates (Q_{org})

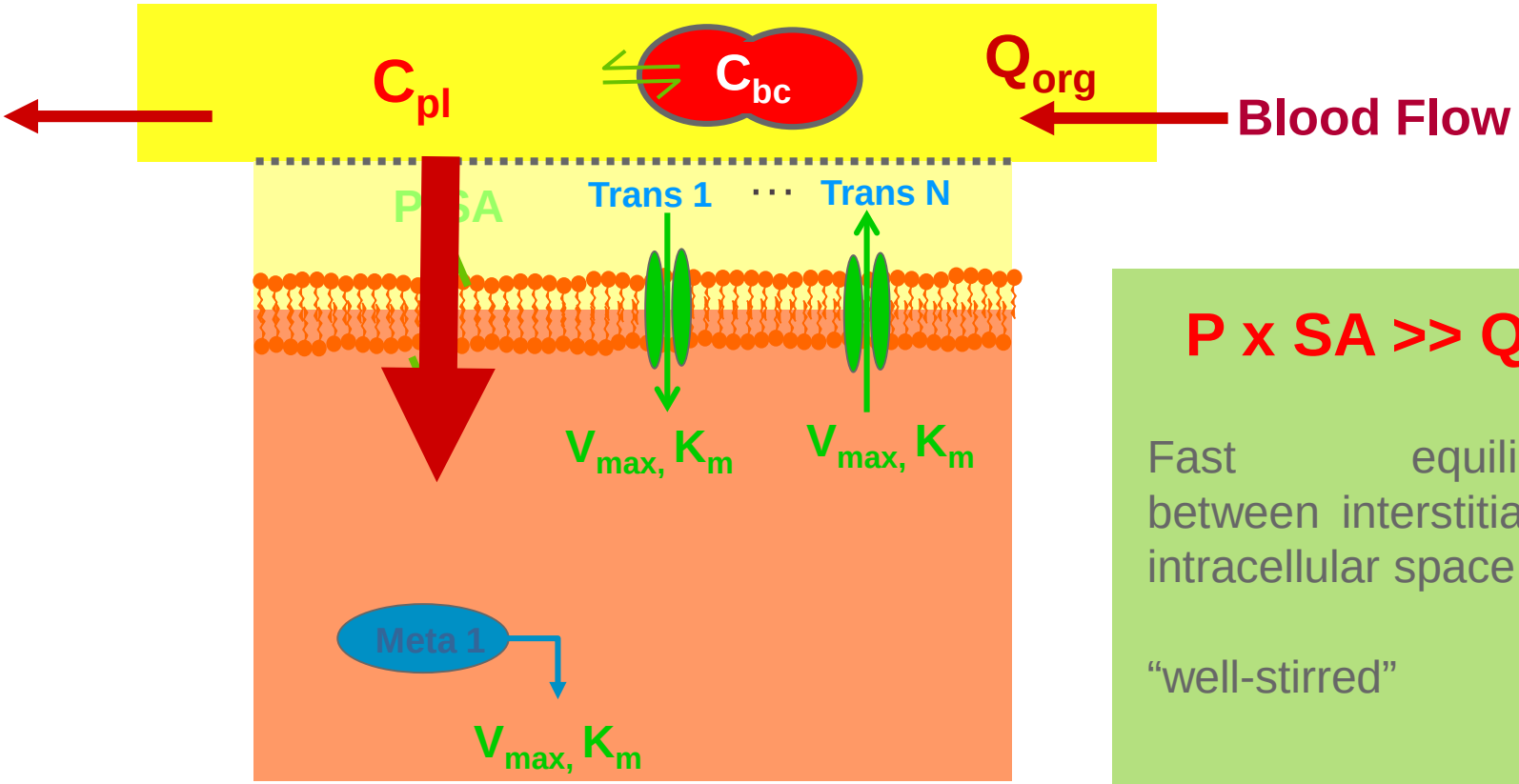
Mixed parameters: Physiology & Substance:

- ⇨ Permeability Surface-Area products ($PxSA_{org}$) → passive diffusion
- ⇨ Organ-Plasma Partition Coefficients → concentration ratio at equilibrium (K_{org})
- ⇨ Metabolic Rates (V_{max}, K_m)
- ⇨ Transport Rates (V_{max}, K_m)



PK-Sim®: Distribution

1.: Blood Flow Limitation



P x SA >> Q_{org}

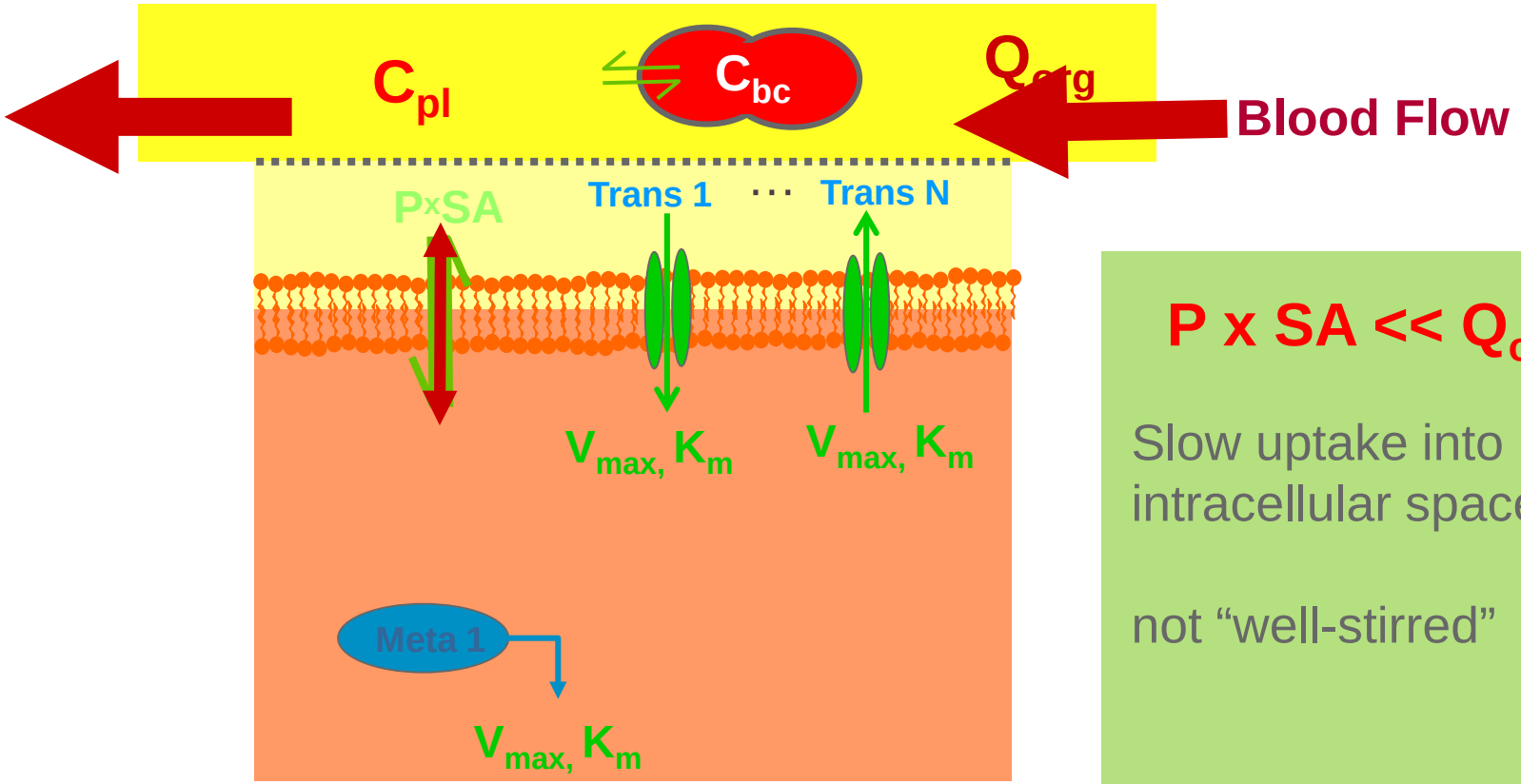
Fast equilibrium between interstitial and intracellular space

"well-stirred"

Willmann et al., *Biosilico* **1(4)**, 121-124 (2003)

PK-Sim®: Distribution

2.: Permeation Limitation



$P \times SA << Q_{org}$

Slow uptake into intracellular space

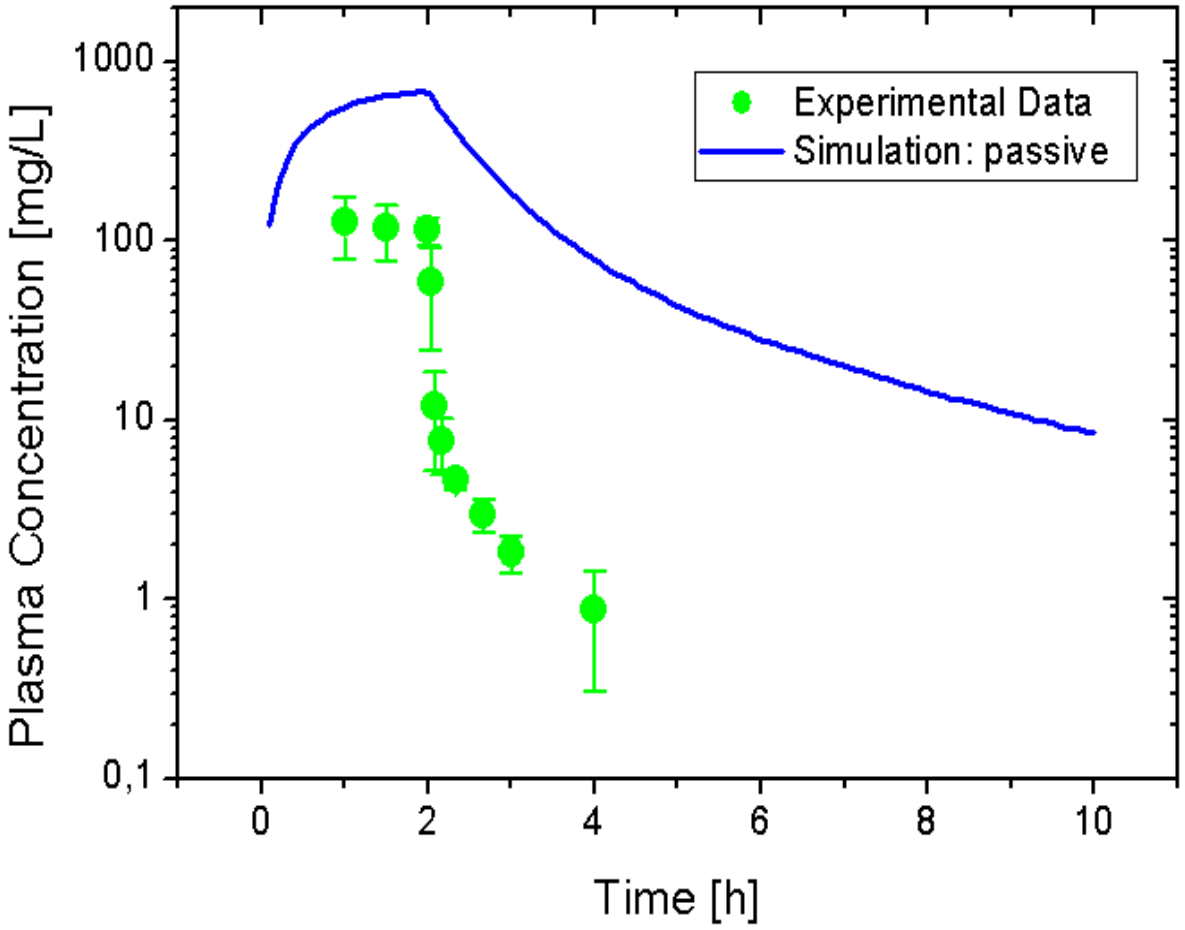
not “well-stirred”

Willmann et al., *Biosilico* **1(4)**, 121-124 (2003)

Understanding PK – Need for a transporter

***Example:* Di-Carboxylic Acid: Substrate for Transporters ?**

Plasma concentration time curve assuming *passive* distribution deviates from experiment.

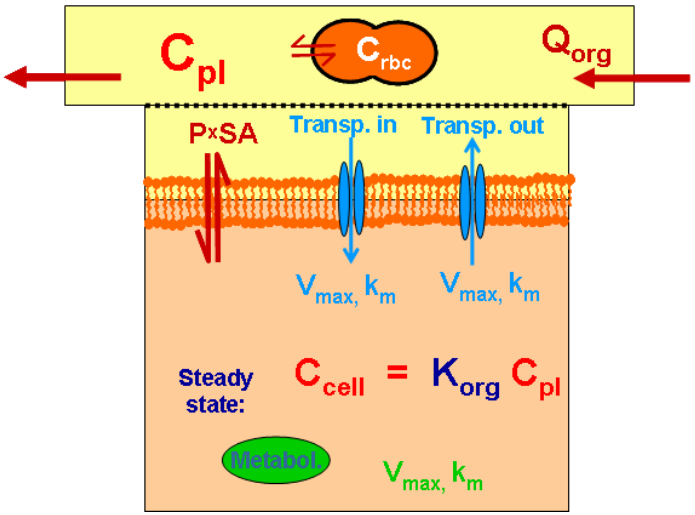


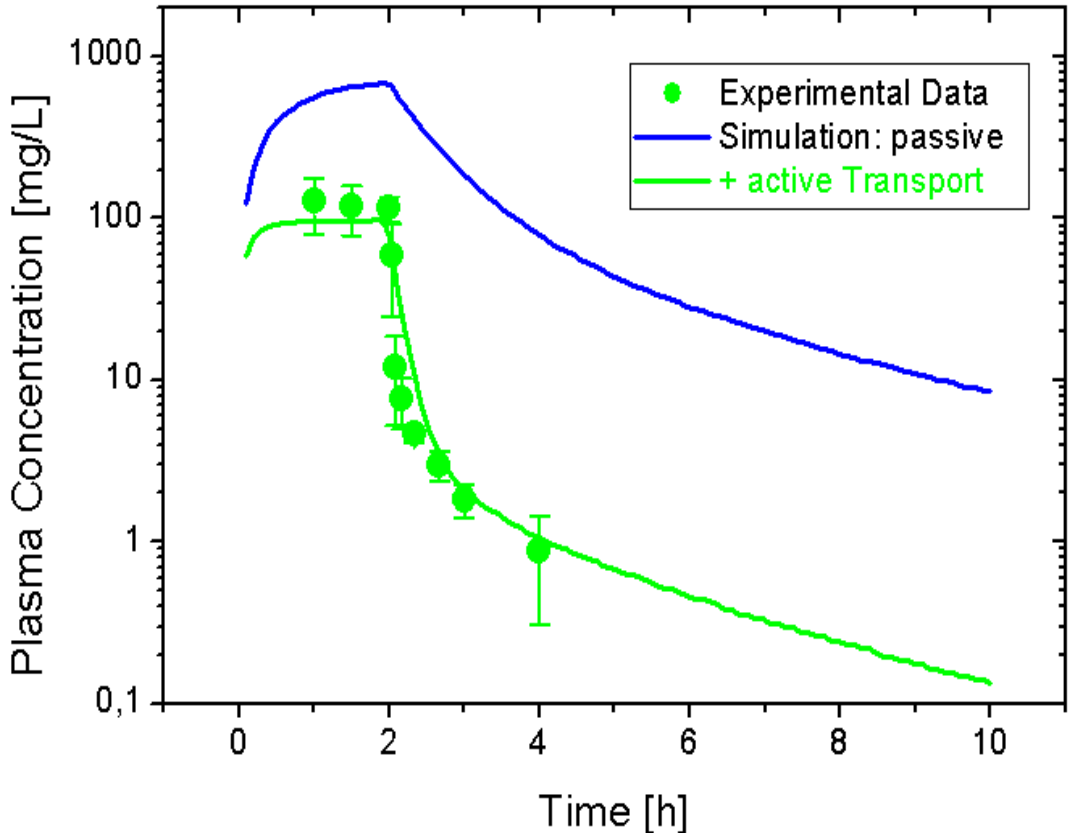
Demo

Understanding PK – Need for a transporter

Example: Di-Carboxylic Acid: Substrate for Transporters ?

Inclusion of an active transport process in the liver yields an almost exact match.





Science For A Better Life

Thank you!

Questions?