



INNOVATION

ENGINEERING

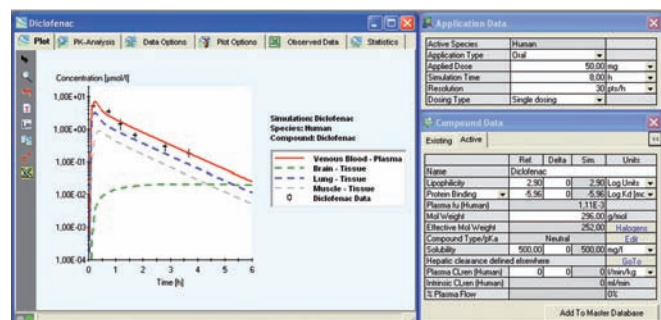
OPTIMIZATION

## The Comprehensive Software Tool for Whole-Body Physiologically Based Pharmacokinetic Modeling

PK-Sim® is a unique software tool for evaluation of absorption, distribution, metabolism and excretion (ADME) properties of drugs by means of whole-body physiologically-based pharmacokinetic (PBPK) modeling and simulation. It allows the straight forward construction of highly specific physiologically-based pharmacokinetic models by incorporation of in vitro and in vivo experimental data and, thereby, to develop a consistent mechanistic understanding of the key processes driving pharmacokinetics.

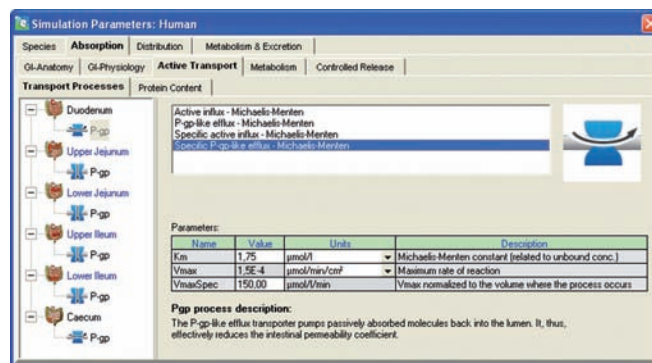
Predefined packages are available for users in different R&D stages: **PK-Sim® Pre-Clinical** for simulating pharmacokinetics of development candidates and **PK-Sim® Clinical** for professional prediction of population kinetics and estimation of age-dependent clearances. In the following, the features of the PK-Sim® Pre-Clinical package are summarized.

**PK-Sim® Pre-Clinical:** This package allows the analysis of mammalian pharmacokinetics following single or multiple intravenous and oral administrations as well as user defined administrations in various organs. The primary result of a simulation run is a set of concentration time curves illustrating the temporal behavior of a drug in the blood and in various relevant organs.



Concentration time profiles in PK-Sim®

PK-Sim® also automatically calculates all major pharmacokinetic parameters and offers the possibility to create and adjust putative substance specific transport processes with saturable kinetics, in all ADME phases. This is essential for many substances, especially for their distribution in the elimination organs and for intestinal uptake. For example, with the help of active transporters one can realize intestinal uptake and hepatobiliary excretion.



Definition of transport processes in PK-Sim®

Furthermore, metabolization reactions can be introduced in any organ to represent organ specific intrinsic clearances. Especially, if the simulated plasma curve does not agree with the experimental data, alternative mechanisms for metabolization reactions and transport processes may be assumed. Thus, PK-Sim® contributes plausibly to the generation of hypotheses and the testing of new mechanisms, such as enterohepatic circulation and organ specific drug metabolism.

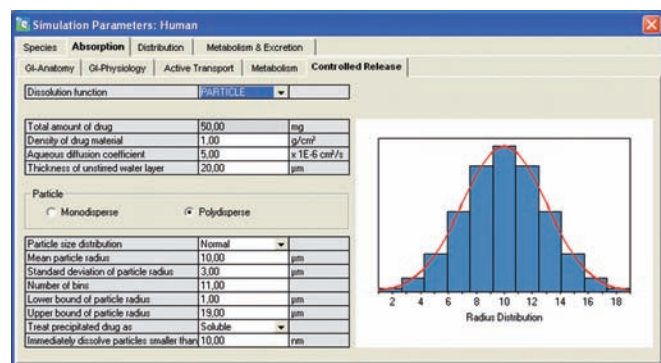
PK-Sim® comprises literature values for all accessible physiological parameters needed for whole body simulations. Substance specific parameters such as permeabilities and partition coefficients are calculated internally from the physico-chemical properties of the substance.



The amount of obligatory input parameters (e.g. values for renal and hepatic clearances) are reduced to a minimum.

## Physiologically-Based Absorption Model

The PK-Sim® Absorption Model enables simulations of the gastrointestinal transit and absorption processes of orally administered dosage forms. Different solution dynamics of solid acids and bases can be handled using an internal solubility versus pH relationship which is automatically created based on user input of substance solubility values at certain pH values. Modified release formulations can be modeled as well. If experimental data of the dissolution process are not available for a direct input, predefined dissolution functions can be used. The other possibility is to simulate the process itself with a given particle size distribution and the physical properties of the dosage form.



Particle size distribution in PK-Sim®

## Physiologically-Based Distribution Model

A major advantage of PK-Sim® resides in the fact that due to the inclusion of permeability and tissue composition, organs are not generally subjected to the 'well stirred' assumption. In fact during the distribution phase, perfusion limitation as well as permeability limitation may occur, distinguishing the distribution behavior for example in the liver from that in the brain, which enhances by far the reliability of the simulations. The distribution of a drug into the peripheral organs, especially into the target organ and into other affected organs, can be easily observed from the corresponding concentration versus time curves.

## Physiologically-Based Elimination Model

Renal and hepatic eliminations are determined by the user defined clearance parameters and occur automatically when a drug distributes through these organs. However, if the interest focuses on metabolism, PK-Sim® allows to model explicit metabolization reactions in the corresponding organs. This is especially useful for the analysis of drug interactions in the liver or in the gut wall.

All these features make PK-Sim® a valuable tool for researchers involved in drug discovery, particularly in biopharmaceuticals and for-

mulation development. An extension of PK-Sim®, namely **PK-Sim® Clinical**, additionally allows for the consideration of subject populations in clinical trials, especially for the consideration of infant populations with adapted physiological parameters.

## Key Features of PK-Sim® Pre-Clinical

- Completely integrated PBPK model describing the key processes of absorption, distribution, metabolization and excretion
- Physiologically-based simulation of gastro-intestinal transit and absorption
- Generation of pH versus solubility tables
- Simulation of the dissolution dynamics of a solid particle formulation with predefined particle size distribution
- Simulation of saturable active uptake and efflux processes as well as luminal degradation and gut wall metabolism
- Permeation limited distribution model
- Minimized requirements for compound specific input data
- Physiological database providing information that mainly depends on age, gender and BMI for different races
- Species database providing physiological data for different animal models
- Graphical user interface for convenient control of simulation parameters
- Calculation of pharmacokinetic data
- Integrated project database for management and storage of data and results
- Import of experimental PK data for convenient and easy comparison with simulation results

## System Requirements

- OS: Vista®, Windows XP®, Windows 2000®
- Processor: Pentium III, 500 MHz
- Memory: 512 MB RAM
- Disk Space: 100 MB

## Integrated Solutions and Services

<b>Products</b>	<ul style="list-style-type: none"> <li>• PK-Sim®</li> <li>• MoBi®</li> <li>• MoBi® Toolboxes for MATLAB® and R</li> </ul>
<b>Services</b>	<p><b>Drug Discovery Support</b></p> <ul style="list-style-type: none"> <li>• Target Identification &amp; Validation</li> <li>• Biomarker Analysis</li> <li>• Proof-of-Mechanism</li> </ul> <p><b>Drug Development Support</b></p> <ul style="list-style-type: none"> <li>• Species Extrapolation</li> <li>• Extrapolation to Special Populations</li> <li>• Proof-of-Concept</li> <li>• Bioequivalence Studies</li> </ul>

For further information on our software tools and services visit our website [www.systems-biology.com](http://www.systems-biology.com).

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