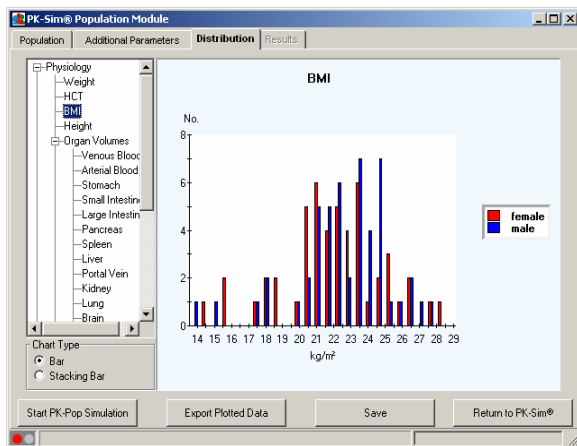


PK-SIM®

The solution for Physiology Based Pharmacokinetic Simulations

Whole-body physiology-based pharmacokinetic (PBPK) simulation is a technique that has been in use for many years to investigate the fate of xenobiotics, particularly drugs, in the human body. Our software package PK-Sim, developed for the detailed analysis of PBPK simulations, has proven its excellence in analyzing and predicting the ADME properties of individual mean subjects. However, in particular during clinical trials of later phases with a large number of subjects the focus of interest is not on one mean individual but on the variability of drug response in a whole population. A prominent issue in clinical trials is the occurrence of subpopulations with a specific drug response behavior. Not only anatomical differences must be taken into account but also enzymatic polymorphisms. Especially the strong age dependence of clearance makes children a major subpopulation with a sophisticated drug response. Due to the explicit consideration of anatomical and physiological properties in PBPK models, they are perfectly suited for the simulation and pre-evaluation of pharmacokinetic variability occurring in clinical trials.



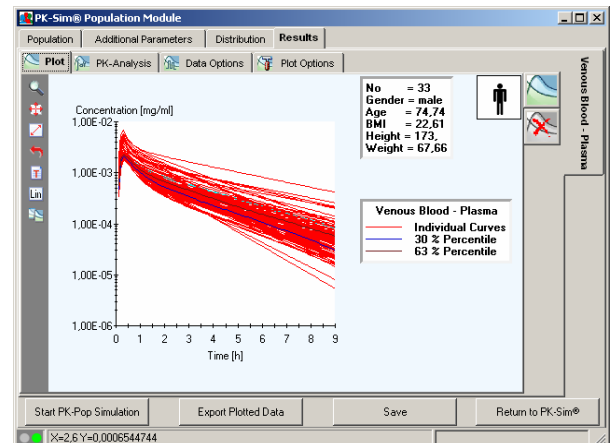
Population Module: Graphical display of distribution

PK-Sim® Clinical as an extension of PK-Sim is especially designed to simulate the pharmacokinetic profiles of a trial population comprising individuals with a certain deviation from the norm. To explicitly include infant populations PK-Sim clinical offers the possibility to adapt renal and hepatic clearances to infant physiology. Your benefit includes an understanding of how the variability in body type, age, and gender relates to deviations from the normal drug response. In addition you may assess the range of drug response which is to be expected and even make predictions about in-

fant pharmacokinetics. As a package, PK-Sim® Clinical is an essential tool for study design and analysis of your clinical trials.

Population-PK Module

At the heart of the Population-PK Module are built in databases containing information about the age and gender dependence of mean values and variability of the relevant anatomical parameters such as body size, organ volume and blood flow (e.g. from the US NHANES III study). The anatomical parameters of virtual individuals are randomly chosen from these empirical parameter distributions.



Population Module: Graphical output of concentration time profiles

For the explicit consideration of special subpopulations, such as obese people, a virtual population can be shifted by the definition of an underlying mean individual.

Another source for deviations in drug response originates from polymorphisms in the drug metabolism of the trial subjects. After the explicit introduction of metabolization enzymes like CYP3A4, this phenomenon can be realized by defining a distribution for the enzyme-related parameters. This feature allows the inclusion of subjects with well-defined pathologies like renal or hepatic impairment into the population simulation.

Clearance Scaling Module

To simulate the pharmacokinetic profiles of children, age dependent infant anatomy is included in the mean individuals of the database. However, the strong age dependence of infant drug response partly arises from



the ontogeny of enzymes, plasma proteins and renal function. The Clearance Scaling Module of PK-Sim Clinical explicitly models infant clearance pathways and automatically scales the clearance to infant ages based on the specification of the adult clearances and the contributions of the eliminating processes involved. Renal clearance is calculated from age depending allometric formulas for renal function parameters (see Hayton 2000). Hepatic clearance is calculated from the adult intrinsic clearances for the different enzymes, which are scaled to infant enzyme activity and liver weight (for the establishment of infant clearance scaling see Edginton et al. 2006). Infant biliary excretion is scaled allometrically to liver weight.

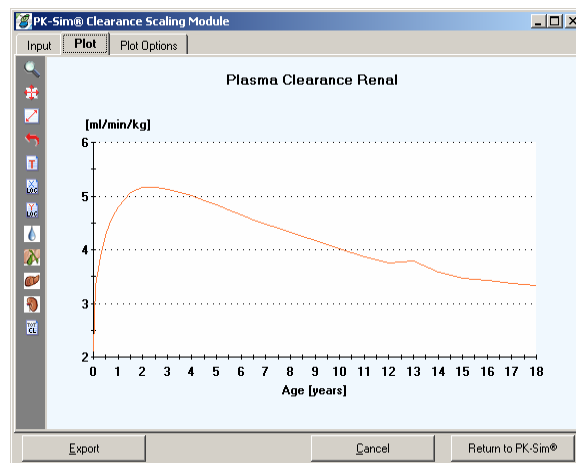
Adult Reference Values	
Plasma fu	0.30
Plasma CLbil	1.00 ml/min/kg
Plasma CLhep	4.00 ml/min/kg
% Blood Flow	20%
Plasma CLren	2.00 ml/min/kg
% Plasma Flow	19%
Adult CL	7.00 ml/min/kg

Age of Interest	
Age	3.00 years
Plasma fu	0.34
Plasma CLbil	2.02 ml/min/kg
Plasma CLhep	6.50 ml/min/kg
% Blood Flow	20%
Plasma CLren	5.13 ml/min/kg
% Plasma Flow	26%
Scaled CL	13.65 ml/min/kg

Hepatic Enzymatic Eliminating Processes	
Enzymatic Process	Proportion
CYP1A2	0
<input checked="" type="checkbox"/> CYP2D6	0.70
CYP2E1	0
<input checked="" type="checkbox"/> CYP3A4	0.30
Sulfation	0
UGT1A1	0
UGT1A6	0
UGT2B7	0

Clearance Scaling Module – Input Window

The full age-dependencies of clearance, from new borns to adults, for a given compound can be displayed.



Clearance Scaling Module - Plot

To conclude, the population simulation module of PK-Sim Clinical is an indispensable tool for risk assessment and study planning in the clinical phase. It is therefore a highly valuable tool in clinical decision making.

Key Features

- ✓ Definition of trial populations by age, gender and body size
- ✓ Scaling of anatomical parameters to body size
- ✓ Random interindividual variability predefined or user defined
- ✓ Minimum, mean and maximum concentration curves, concentration density plots
- ✓ Median and percentile curves
- ✓ Statistics of pharmacokinetic parameters
- ✓ Distribution plots for pharmacokinetic parameters

System Requirements

- OS: Windows XP, Windows 2000
- Processor: Pentium III, 500 MHz or better
- Memory: 256 MB RAM
- Disk Space: 40 MB

Integrated Solutions and Services

BTS offers an integrated suite of products including:

- PK-Sim
- MoBi

These tools build the platform for our services in the field of mechanistic modeling and simulation:

- ADME Simulation
- Biological Network Modeling
- Evaluation of Drug and Licensing Candidates
- Drug Response Prediction

Contact

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