Development of a Physiology-Based Population Pharmacokinetic Approach for the planning of Clinical Studies

Walter Schmitt [1], Karsten Höhn [1], Juri Solodenko [2], Michael Sevestre [2], Jörg Lippert [2], and Stefan Willmann [1]

[1] Bayer Technology Services GmbH, Process Technology, Competence Center Biophysics, D-51368 Leverkusen, Germany

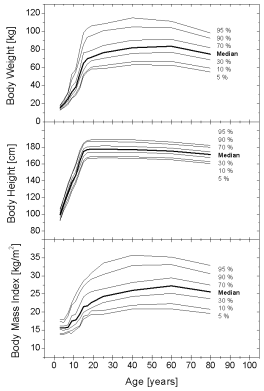
[2] Bayer Technology Services GmbH, Process Technology, Competence Center Computational Solutions, D-51368 Leverkusen, Germany

INTRODUCTION

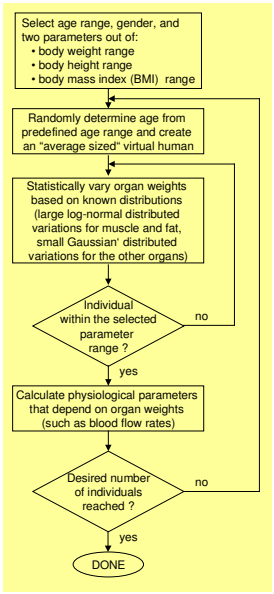
We have developed a population module for our physiology-based pharmacokinetic (PBPK) whole body simulation tool PK-Sim® [1,2]. In its current version, PK-Sim® simulates the pharmacokinetic profile of an average sized male individual (by default, all parameters can be varied by the user). The idea of the population module is to expand the database of human physiological properties in PK-Sim® to variations in realistic populations covering a wide age range and to use a Monte-Carlo approach to simulate whole (sub-)populations. Such a physiology-based population approach can be very useful for the planning of clinical studies.

METHODOLOGY

In order to perform PBPK simulations in a realistic human population, the variabilities of the relevant physiological parameters, such as organ weights, blood flow rates, etc., must be known. Valuable sources for this information are the NHANES study [3] or the *Annals of the ICRP* [4]. The right Figure shows the reported variability of body weight (BW), height (BH), and body mass index (BMI) for a north-American, caucasian male population in the age range between 3 and 80 years [4] (the collection of this data for neonates and young infants is ongoing).

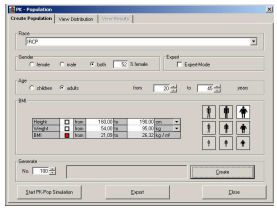


Based on this information, a virtual population is created by means of a statistical Monte-Carlo approach. The flowchart demostrates the workflow for the population module. First, the age range and gender of the individuals must be defined. Then, "average sized" individuals are created according to the known age distribution of BW, BH, and BMI. The organ weights of these average sized individuals are then statistically varied (again based on known distributions reported in the literature [3,4]). For all organs, Gaussian distribution can be assumed except for muscle and fat tissue, which are log-normally distributed. The variability in muscle and fat content mainly contributes to the overall log-normal distribution of BW and BMI in a realistic population [3,4]. In addition, certain pathological conditions such as renal or hepatic impairment, gastro-intestinal disorders, etc. can also be described within the population module.



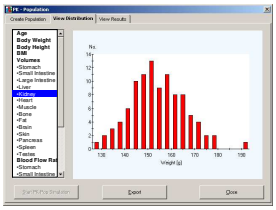
SCREENSHOTS OF THE POPULATION MODULE

a) Create Population Window



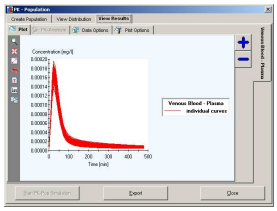
In the Create Population Window, the basic parameters that describe the virtual population are defined. Gender, age range and a combination of BW, BH, or BMI can be chosen. Icons with tall/short and slim/overweight humans visualize the composition of the virtual population. The creation of a population of 1000 individuals takes approximately 20 seconds.

b) View Distribution Window



The frequency distributions of the relevant physiological parameters (organ weights, blood flow rates, etc) are shown in this window.
If the virtual population represents the desired population, a batch mode is started that runs all individual simulations successively. Otherwise, the population data can be disregarded and a new population can be created.

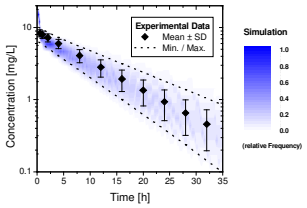
c) Results Window



When the batch simulations are finished, the simulation results can be displayed as individual concentration-time curves, statistical curves (mean, s.d., median, percentiles) or in form of density plots (see example below). The physiological parameters of each individual curve appear on demand.

EXAMPLE: THEOPHYLLINE PLASMA PK

Using the population module of PK-Sim®, the plasma pharmacokinetics of Theophylline was simulated in 16 healthy male volunteers (aged 20 to 41 years) after a 20 min. intravenous infusion of 5 mg/kg. The graph shows the simulated data in form of a density plot. Experimental mean ± s.d. [symbols], minimum and maximum concentrations [dotted lines] are shown for comparison [5]:



As can be seen, the population module reliably describes the *in vivo* distribution of Theophylline plasma concentrations in this population.

POTENTIAL APPLICATIONS OF POPULATION-PBPK MODELING

The population module of PK-Sim® is particularly useful in the clinical phase of drug development. Other potential applications include:

- ***Better estimation of the first-dose-in-man:*** Prior to clinical phase I, laboratory animal data must be scaled up to humans in order to determine the dose for the first-in-man studies. Using the population approach, the range of variability that is expected in a real population can be determined.
- ***PK-Predictions in certain sub-populations:*** Contrary to the healthy volunteers investigated in clinical phase I, real patients often suffer from a number of pathological conditions. Many of these can be accounted for in population-PBPK modeling, e. g. obesity, metabolic disorders, renal impairment.
- ***Assessment of the PK behavior in children:*** Clinical studies in pediatric populations are difficult to perform for ethical reasons. PBPK population approaches are well suited for extrapolating adult PK profiles to children using a rational, physiological basis.

SUMMARY AND CONCLUSIONS

We have extended our physiology-based pharmacokinetic (PBPK) modeling tool PK-Sim® to simulate the expected pharmacokinetic behavior of drugs or drug-like substances in a virtual human population. As in PK-Sim®, a convenient graphical user interface allows the definition of the characteristics of this population. The age-dependent physiological data relevant for PBPK simulations have been collected from literature sources [3,4]. Currently, the age range from 3 to 80 years can be modeled. Output data includes individual as well as statistical PK information (concentration-time curves and derived PK parameters).
The comparison between experimental plasma concentration-time data of Theophylline and corresponding simulations in a population of healthy male volunteers demonstrated excellent agreement. The technology of population PBPK modeling is particularly useful in the clinical phases of drug development.

REFERENCES

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Dr. Stefan Willmann
Bayer Technology Services GmbH
51368 Leverkusen
Germany
Stefan.Willmann@bayertechnology.com

Fax: +49 (0)2173 38 969 4546