Chapter 2

Scope and intent of the investigations in this thesis

Special populations is a general term referring to groups of patients that may respond differently to drug treatment as a result of a variety of factors, such as age and disease. The diversity of the special populations often requires the performance of dedicated clinical studies to support dose labelling as required by regulators. Frequently, these first clinical studies in special populations are studies into the PK, of which the results are then used to extrapolate efficacy and safety data from pivotal study populations to special populations. Complicating factors in the performance and/or analysis of these studies are the ethical barriers, the population heterogeneity, the relatively small sample sizes and the limited data that can be collected. Altogether, these factors can undermine the objective of the study when not well designed. Therefore, the application of model-based approaches becomes essential for prediction of the pharmacokinetics (PK) in special populations, to inform the clinical study design and to ensure that knowledge is not lost in the transition from prediction to data analysis.

For prediction of (variation in) PK in special populations, the traditionally used model-based approaches are: compartmental PK modelling and physiology-based pharmacokinetic (PBPK) modelling. Compartmental PK modelling is a data driven approach with a statistical basis that enables optimisation of the clinical study design and that constitutes a basis for the analysis of the data by nonlinear mixed effects regression analysis. Compartmental PK models can be combined with allometric equations to account for differences in size in the prediction of the PK in children and adolescents. To account for both differences in size and in maturation (i.e. of drug elimination processes), allometric scaling combined with a maturation function has been proposed to predict the PK in neonates and infants. However the accuracy of this approach has not been established. In contrast, PBPK modelling is a knowledge driven approach with a strong physiological basis that in principle enables prediction of the PK in various special populations. Its inherent complexity, however, limits the application in combination with non-linear mixed-effects regression techniques and thereby the use of these techniques for optimisation of the study design and the analysis of the results of clinical studies. It is postulated that the development of a framework that integrates the physiological basis of the PBPK models with the statistical utility of the compartmental PK models opens new perspectives in the design and evaluation of clinical studies in special populations.

In this thesis, we aimed to develop a semi-physiological PK framework which was designed

(i) to preserve the physiological foundation of PBPK modelling in order to maintain the predictive power and to allow prediction of the PK into various special populations and

(ii) to reduce model complexity to enable the application of non-linear mixed effect regression techniques to optimise the study design and to analyse the data.

The concepts and the development of this semi-physiological framework are presented in **section 2** (**chapter 3** and **chapter 4**) and its applications are described in **section 3** (**chapter 5** and **chapter 6**).

In **chapter 3**, the interchangeability of the traditionally used model-based approaches to predict the clearance in children (i.e., allometric scaling and PBPK modelling) is investigated. The analysis focused on the allometric scaling maturation functions that were established using paediatric clinical PK data of paracetamol and morphine after intravenous administration. First, the estimated allometric scaling maturation functions were compared with the maturation functions of the liver enzymes as used in the PBPK models. Second, for hypothetical drugs with different PK properties, absolute clearance predictions obtained using allometric scaling in combination with maturation functions were compared to PBPK predictions. Finally, the accuracy of the predictions using PBPK modelling for paracetamol and morphine was evaluated using the PK parameter estimates of compartmental PK models in combination with allometric scaling as reference. The results of this investigation showed that allometric scaling maturation functions do not solely represent ontogeny of enzyme activity, but aggregate multiple PK properties, as for example extraction ratio and lipophilicity (log P). Furthermore, predictions of clearance using PBPK modelling were shown to underestimate the inter-individual variability probably because this approach does not take unknown sources of variability into account.

In **chapter 4**, the prediction of clearance in paediatrics is examined for accuracy. A literature database of 18 CYP3A-metabolised compounds was compiled containing 203 clearance values in patients ranging from term-neonates to adults. The clearances in adults were scaled to children using (i) allometric scaling plus maturation function and (ii) a mechanistic approach based on the well-stirred model of hepatic clearance. Three maturation functions were separately evaluated. In children >3 months, all approaches yielded very similar predictions for clearance, for each of the three maturation functions that had been studied. Biases were mostly observed in children <3 months. Only the mechanistic approach using an overall-CYP3A maturation function in conjunction with the well-stirred model of hepatic clearance, led to unbiased predictions of clearances across all ages. Yet, the high individual percentage errors and the relatively low 2-fold percentage error (percentage of the observations within two fold of the median prediction) observed when the well-stirred model was applied underlined the need for considering inter-individual variability in the predictions.

Altogether, the results described above indicate that the application of the allometric scaling for the prediction of clearance may be restricted to children in the age range where there is no ongoing maturation of physiological processes and in whom PK is not affected by disease. Also, the inter-individual variability was shown to be inadequately predicted not only by allometric scaling but also by PBPK modelling. This underscores the need for the development of a framework which combines (i) a physiological basis for the prediction of the PK in special populations and; (ii) reduced complexity to allow combination with nonlinear mixed-effects modelling and thereby better prediction of the unknown sources of variability. To develop the model structure of the framework, the mechanistic approach based on the well-stirred model for prediction of clearance is proposed.

In **section 3** of the thesis the emphasis is on the application of a semi-physiological PK framework that is based on the interfacing of a compartmental PK model with physiological equations (mostly based on well-stirred model of hepatic clearance) to predict changes in PK in special populations. An

important principle is that the selection of the exact features and the complexity of the semi-physiological PK model are based on the purpose of the model (i.e. the proposed models are "physiological fit for purpose" models). Another important feature is that the semi-physiological PK models are capable to adequately predict the time course of the drug concentration as well as the inter-individual variability in the target population. Here the inter-individual variability is predicted on the basis of two components: (i) the variability in the key physiological parameters which can be calculated by means of anthropometric equations and; (ii) the remaining variability that is determined by unknown sources and which can be estimated by the model.

In **chapter 5**, a semi-physiological PK model is developed for prediction of the influence of hepatic and renal impairment on the PK of solifenacin as a paradigm drug. The proposed model is based on a compartmental partitioning framework to account for binding to plasma proteins and to non-plasma tissues, combined with mathematical expressions describing the main PK processes, i.e., first-pass effect, distribution, and elimination. This allowed quantification of the impact of key physiological parameters (i.e., body composition, glomerular function, liver enzyme capacity and liver blood flow) on the PK of solifenacin. In addition, in **chapter 6**, an adapted version of this model is applied to evaluate the influence of growth related factors on the PK of tamsulosin in children in the age range from 6 to 12 years Here prediction of the time course of the drug concentration in the special populations only requires adjustment of the physiological parameters to values in the range that is observed in special populations without modifying the model structure and/or its respective system specific parameter estimates. The adequacy of the semi-physiological PK model is evaluated on the predictions of both average and inter-individual variability.

Chapter 7 discusses the main findings and the general conclusions of the investigations described in this thesis along with the perspectives for the future application of the semi-physiological PK model. It is concluded that semi-physiological PK models constitute a scientific basis for the prediction of variation in the time course of the drug concentrations in special populations and for the application of optimal design concepts for optimisation of first in special population clinical studies. A unique application could be the prediction of the changes in PK in situations where multiple factors in combination (i.e. ageing and disease) have contributed to the variation in PK.