Chapter 2

Scope and intent of the investigations

2.1. Background and introduction

In pharmacokinetics, drug clearance is an important parameter that characterizes the rate of elimination from the circulation. The value of clearance constitutes the basis for dose selection in clinical practice. During growth and development of a human being, there are many physiological and anatomic changes resulting in varying drug clearance in the paediatric population, with values typically differing substantially from drug clearance in the adult population. The need to optimize the dose in children warrants detailed investigations into the variation in drug clearance in the paediatric population.

Population modeling and simulation constitutes a scientific basis to characterize inter-individual variation in pharmacokinetics. An important feature of population modeling is the possibility to attribute the variability between individuals in the observed drug concentrations to the variability in the values of different pharmacokinetic parameters. The latter variability may in its turn be explained by variables that are related to physiological volumes and functions, e.g. weight or age, in a so-called covariate analysis. This data-driven modeling approach provides us pertinent information on the variation in clearances over the whole paediatric age-span based on clinical observations. A limitation of population pharmacokinetic analysis is that it does not enable predictions on the variation in clearance beyond the drugs and the conditions that have actually been studied.

At present, there is great interest in the use of physiologically based pharmacokinetic (PBPK) for the prediction of variation in drug clearance paediatric populations [1-3]. An important feature of PBPK models is their physiological basis. As a result they enable prediction of the variation in pharmacokinetics of drugs that have not been studied, based on known information on changes in physiological function. However, due to the difficulty of collecting *in vitro* data in children, e.g. enzyme activity in neonates, the knowledge of physiological processes is missing for some paediatric populations, making the PBPK model less reliable in simulating PK profiles in those populations.

Ideally, the best paediatric pharmacokinetic model should be able to not only fit the clinical observations but also explain the physiological mechanism. A combination of the POPPK and PBPK is naturally the best solution. It is proposed

that PBPK models are refined by the results of covariate functions from POPPK models of probe drugs sharing the same physiological mechanism. Moreover, with the help of POPPK model, physiological parameters in PBPK models can be scaled to certain paediatric populations where no *in vitro* information available. Therefore, developing a POPPK model covering the age-span from birth to adult with good descriptive performance all across is of great value.

Amongst currently used top-down population pharmacokinetic models, neither the ¾ allometric scaling model nor its derivative maturation model can describe the developmental changes in drug clearances with adequate statistical stability and predictive performance overall across the entire age-span. In this thesis we present a novel approach to describe the developmental changes in pharmacokinetic parameter estimates across the entire human lifespan, specifically focusing on drug clearances.

2.2. Outlines of the thesis

In **Chapter 3**, we studied the developmental changes in the clearance of propofol in various age groups, ranging from preterm neonates to adults. The emphasis was on estimation of the value of the allometric exponent in distinct age ranges. To this end, a large database was established comprising data obtained in neonates, infants, toddlers, children, adolescents and adults. Next, the allometric exponent was estimated when scaling clearance between two different paediatric subgroups or between one paediatric group and one adult group. With the pre-specified allometric equation, the values of the exponent were found to vary depending on the combination of the selected paediatric subgroups. Interestingly, the values of the allometric scaling exponent were larger than 1 when the subgroup with neonates was included in the analysis. From this analysis, it is concluded that there is no single value of the allometric exponent that describes variation in clearance across the entire human lifespan.

In **Chapter 4,** we introduced a novel approach to describe developmental changes in clearance across the human lifespan from preterm neonates to adults, based on the concept that "the allometric exponent varies with bodyweight". To this end data on the clearance of propofol were analyzed with

different covariate models to describe developmental changes in clearance. The covariate models that were considered were: i) a mixture model, ii) a cut-point model and iii) a bodyweight dependent exponent (BDE) model. In this analysis the BDE model was found to yield the best description of the changes in clearance across the whole paediatric age-span.

In **Chapter 5** the BDE model was applied for the scaling of the total clearance of morphine, clearance to M3G and clearance of M3G across preterm neonates, children, adolescents and adults. It succeeded in describing those clearances without including additional age covariates, which were found to be necessary in model developed before. In this study, we also demonstrated the BDE model can be used not only for parent drug but also for its metabolites.

In **Chapter 6**, we further tested the BDE model in describing paracetamol clearance across whole paediatric age-span, which had been modeled with different covariates in the past. Again, it was clearly proved that for data across the human lifespan, the BDE model is able to describe the age-related changes in clearance very well without the need for additional age variables. Visual comparison among model predicted clearances from different models showed the BDE model had adequate descriptive performance of clearance throughout the whole paediatric age-span, whereas other models could only perform well in part. Based on the final model, simulations were performed to derive optimized dosing guidelines for paracetamol across the entire paediatric age range including preterm neonates.

In the meantime, a simplified version of the BDE model was successfully implemented for three other drugs: busulfan, midazolam and antibiotics. The results of these analyses are presented in the **appendices I - II**. The simplified BDE model is still based on the concept of using a monotonous continuously decreasing function of bodyweight to express age related changes in allometric exponent with bodyweight. The simplified BDE model may be better suited than the full BDE model in cases where preterm or term neonates are not included, or when the drug is metabolized by the CYP450 3A iso-enzymes or renally cleared by the kidney.

In **Chapter 7**, general conclusions and future perspectives of the work presented in this thesis were discussed.

References

1. Johnson TN, Rostami-Hodjegan A. Resurgence in the use of physiologically based pharmacokinetic models in pediatric clinical pharmacology: parallel shift in incorporating the knowledge of biological elements and increased applicability to drug development and clinical practice. Paediatr Anaesth 2011; 21: 291-301.
2. Edginton AN. Knowledge-driven approaches for the guidance of first-in-children dosing. Paediatr Anaesth 2011; 21: 206-13.
3. Barrett JS, Della Casa Alberighi O, Laer S, Meibohm B. Physiologically based pharmacokinetic (PBPK) modeling in children. Clin Pharmacol Ther 2012; 92: 40-9.