How to scale clearance from adults to children for drugs undergoing hepatic metabolism? Insights from advanced PBPK modelling and simulation

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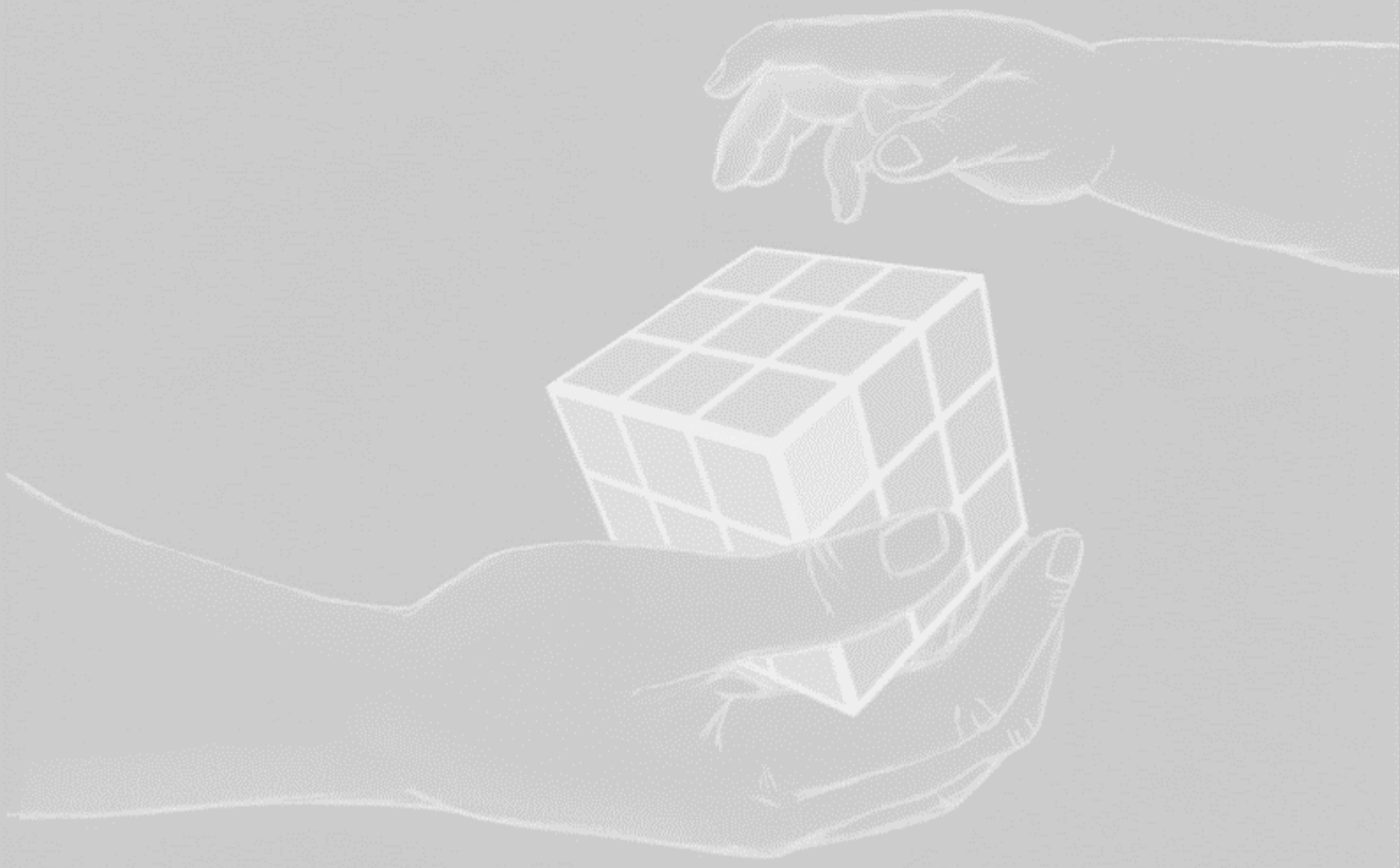
Chapter 2

Scope and intent of the investigations



Clearance is a key parameter for efficacious dose tailoring in paediatric patients. This pharmacokinetic parameter undergoes ontogenic changes, which can be quantified across the paediatric age range using model-based approaches. Models describing ontogenic changes in clearance are the basis of individualized therapy, ultimately preventing variability in drug exposure across the paediatric age range. Such models should be developed and validated on paediatric clinical data in order to ensure safe and efficacious drug treatment. However, such data is lacking for many marketed drugs and for first-in-child clinical trials, leaving many children potentially over- or under-dosed. To ensure safe and efficacious dosing while coping with this lack of data, information on clearance ontogeny across the paediatric age range is obtained using scaling functions which rely on covariates such as weight and/or age. Often, paediatric clearance is scaled from previously measured adult values, since adult data is generally available before undertaking paediatric clinical trials. To date, a diversity of scaling functions has been proposed to scale clearance across the paediatric population. These models require different extents of information for their application.

While Physiologically-Based PharmacoKinetic (PBPK) is the best scaling method to accurately scale clearance across the paediatric age range in absence of paediatric clinical pharmacokinetic data, this approach is time consuming, requires specific expertise and sometimes necessitates the conduct of *in vitro* or *in vivo* experiments. Simpler scaling functions represent a valuable alternative to expedite clearance scaling from adults to children, since they require less information and can be used without extended training. While there are many simple scaling methods available (Chapter 1, Table 1), a clear overview of their applicability is lacking, leaving clinical pharmacologists without guidance on how to best extrapolate clearance from adult to paediatric patients.

Accuracy of these scaling methods depends on their ability to aggregate the influence of ontogeny in diverse system-specific parameters impacting paediatric clearance for diverse drugs (Chapter 1, Figure 2). This can be investigated using PBPK simulations of clearance ontogeny of diverse drugs across the paediatric age range [1], since paediatric PBPK models link ontogeny in system-specific parameters and drug properties with clearance ontogeny. Developing a decision tree for a rational choice of appropriate clearance scaling methods would ensure accurate clearance scaling while using the minimum amount of prior data, which would ultimately facilitate and accelerate paediatric dose tailoring and would steer efforts of future research in this field. While PBPK models represent a valuable tool to understand important ontogenic changes that should be accounted for to accurately predict clearance

ontogeny of diverse drugs, further development of these models for different understudied paediatric populations is needed. Therefore, the aim of this thesis is to expedite and ensure the systematic accuracy of clearance scaling from adults to paediatric patients, with a special focus on drugs undergoing hepatic metabolism.

In **Section II**, using a PBPK-based simulation workflow, we systematically investigate two methods that scale clearance by solely accounting for bodyweight differences across the paediatric age range. The accuracy of clearance scaling from adults to different paediatric ages, from term neonates of one day to adolescent of 15 years, is investigated for both drugs undergoing hepatic metabolism and drugs undergoing glomerular filtration presenting a wide range of drug properties. Scenarios for which these scaling methods systematically lead to accurate paediatric clearance predictions are defined in order to guide their use. **Chapter 3** specifically investigates allometric scaling using a fixed exponent of 0.75 (AS0.75). Additionally, in this chapter, drugs for which clearance ontogeny is only influenced by size-related changes are selected, and the value of the allometric exponent scaling the clearance of these drugs from adults to the different investigated paediatric ages is estimated. This is performed in order to investigate the strong belief that size-related changes scale with a unique allometric exponent of 0.75 across the paediatric age range. **Chapter 4** specifically investigates allometric scaling using a fixed exponent of 1, also known as linear scaling. This simple scaling method is often used to adapt paediatric doses from adult dosing in the clinic when no dosing guidelines are available. Additionally, in this chapter, scaling accuracy of linear scaling is compared to scaling accuracy of AS0.75.

In **Section III**, using the same PBPK-based simulation workflow, we systematically investigate the accuracy of scaling methods accounting for age-related changes in general or ontogeny in hepatic isoenzyme responsible for drug clearance. Scenarios for which these scaling methods systematically lead to accurate paediatric clearance predictions are defined in order to guide their use. **Chapter 5** identifies conditions for which extrapolation of covariate models between drugs sharing the same elimination pathway consistently leads to accurate clearance scaling from adults to different paediatric ages, from term neonates of one day to adolescent of 15 years. Because population PK covariate models are the basis of dose recommendations, this investigated scaling approach could also allow for extrapolation of paediatric dosing recommendations from a drug of which the changes in clearance have been quantified to other drugs for which no paediatric PK studies have been undertaken, provided these drugs share the same elimination pathway. Since most drugs are metabolized by several

isoenzymes, the impact of elimination through multiple elimination pathways on drug clearance is assessed.

Chapter 6 systematically assesses and compares the scaling accuracy of age-dependent exponent (ADE) [2] and AS0.75+MF_{PBPK} [3] in children younger than five years for drugs undergoing hepatic metabolism. These two scaling methods have been proposed to circumvent the reported inaccuracy of AS0.75 in young children, which is believed to be due to maturational processes occurring simultaneously with growth at young ages [4–6]. ADE relies on the use of different allometric exponents for different age groups, and is proposed to scale clearance of any drugs, disregarding their route of elimination. AS0.75+MF_{PBPK} scales bodyweight-dependent changes in clearance based on AS0.75 and age-dependent changes in clearance based on isoenzyme ontogeny functions as implemented in PBPK models. AS0.75+MF_{PBPK} is a scaling method for drugs undergoing hepatic metabolism and is a more flexible function than ADE since it accounts for the different ontogeny patterns of isoenzymes responsible for drug clearance. Comparison of these two methods allows for the assessment of whether specific ontogeny patterns of different isoenzyme pathways are needed for accurate clearance predictions in young children.

In **Section IV**, **Chapter 7**, we propose the estimation of key PBPK parameters based on clinical data using population modelling as a solution to circumvent the lack of data on system-specific parameters of PBPK models which imped their development for specific paediatric subpopulations. We develop a methodology to investigate the feasibility and requirements for precise and accurate estimation of PBPK parameters using population modelling of clinical data and illustrate this for two key PBPK parameters for hepatic metabolic clearance, namely whole liver unbound intrinsic clearance and hepatic blood flow in children.

In **Section V, Chapter 8**, results and conclusions of this thesis are summarized and discussed and a decision tree for the applicability of the scaling methods investigated is provided based on the results of this thesis. Moreover, future perspectives are presented. Perspectives are given concerning the use of the decision tree to select an appropriate clearance scaling method and ideas are provided to enable further improvement of paediatric PBPK models to extend their use to understudied drugs and patient populations. Finally, we provide good modelling practice for the estimation of the allometric exponent to scale both size- and age-related changes in clearance.

References

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Section II

Scaling methods based on bodyweight to extrapolate adult clearance to paediatric patients