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

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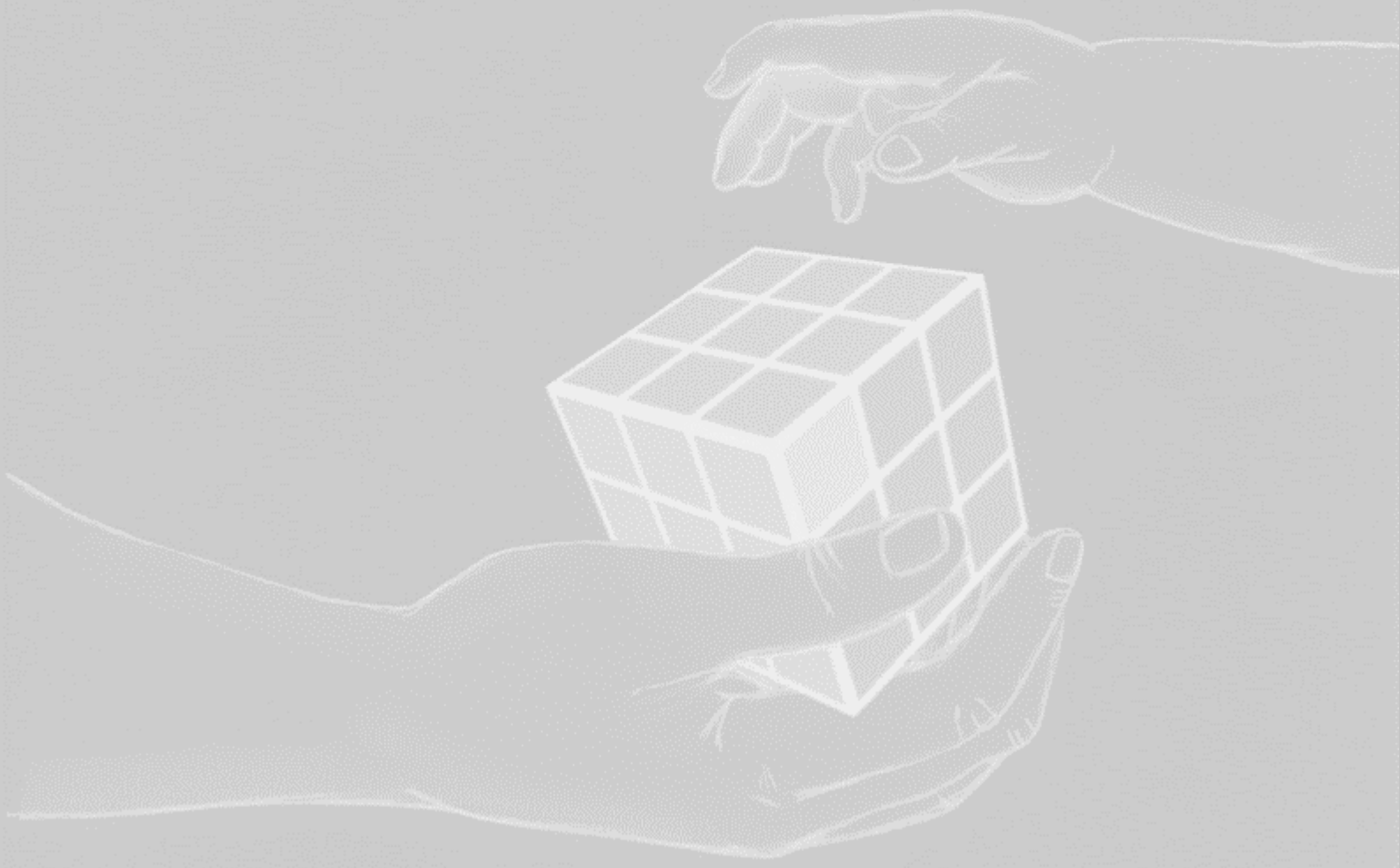
Chapter 8

Scaling clearance from adults to the paediatric population: Summary, conclusions and perspectives



8.1. Summary

Clearance scaling allows to derive clearance values across the paediatric age range based on adult clearance values and, ultimately, to derive paediatric dosing regimen in absence of (sufficient) paediatric clinical data. Accuracy of clearance scaling methods depends on their ability to aggregate the influence of ontogeny in diverse system-specific parameters impacting paediatric clearance for diverse drugs. Because Physiologically-Based PharmacoKinetic (PBPK) models allow to link ontogeny in system-specific parameters and drug properties with clearance ontogeny, in **section II** and **section III** of this thesis, using a new PBPK-based simulation workflow, the systematic accuracy of scaling methods was investigated across the paediatric age range for a wide range of drugs. This workflow unravelled paediatric age ranges and drug properties for which the different scaling methods efficiently aggregate important mechanistic information, thereby leading to systematically accurate paediatric clearance predictions. The investigations of **section II** and **section III** have thereby unravelled how clearance can be accurately scaled from adults to children with a minimum but necessary amount of information, with a focus on drugs undergoing hepatic metabolism, which is summarized by a paediatric clearance scaling decision tree in this concluding chapter. Moreover, we challenged beliefs about the universality of an allometric exponent to scale clearance across the paediatric age range (**chapter 3, 4** and **6**), and translated these findings into clearance ontogeny good scaling practice in this chapter.

PBPK models are essential to scale clearance of specific drugs in different paediatric ages and allow for the investigation of the accuracy of other scaling methods as illustrated in **section II** and **section III**. However, PBPK models may not be comprehensively available and/or reliable for all paediatric sub-populations, such as critically ill children, preterm neonates or obese children. In addition, these models require extensive *in vitro*, *ex vivo* and/or *in vivo* data for their development as well as a time consuming learn and confirm cycle for their validation [1,2]. In order to overcome these hurdles and ultimately develop PBPK models for understudied populations, we propose, in **section IV**, the direct estimation of PBPK parameters based on clinical PK data. Because of the challenges related to the application of this method, we developed in this section a new analysis framework based on optimal design principles, in order to investigate the feasibility and design requirements to estimate PBPK parameters based on clinical data using population PK (popPBPK) modelling.

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

In **chapter 3**, a systematic assessment of the applicability of allometric scaling on the basis of bodyweight raised to the power of 0.75 (AS0.75) was undertaken for scenarios considering size-related changes with and without maturation processes. These two scenarios were investigated since, based on strong beliefs, AS0.75 is frequently used to scale size-related changes in total (i.e., bound and unbound) plasma clearance (CLp) from adults to children and important prediction bias reported in young children with this scaling method is often attributed to the maturational processes occurring simultaneously with growth at young ages. A PBPK simulation workflow was developed in R for 12,620 hypothetical drugs. In scenario one, only size-related changes in liver weight, hepatic blood flow, and glomerular filtration were included in simulations of 'true' paediatric CLp. In a second scenario, maturation in unbound microsomal intrinsic clearance (CLint,mic), plasma protein concentration, and haematocrit were also included in these simulated 'true' paediatric CLp values. For both scenarios, the prediction error (PE) of AS0.75-based paediatric CLp predictions was assessed, while, for the first scenario, an allometric exponent was also estimated based on 'true' CLp. In the first scenario, the PE of AS0.75-based paediatric CLp predictions reached up to 278% in neonates, and the allometric exponent was estimated to range from 0.50 to 1.20 depending on age and drug properties. In the second scenario, the PE sensitivity to drug properties and maturation was highest in the youngest children, with AS0.75 resulting in accurate CLp predictions above 5 years of age. Below the age of 5 years, the PE is dependent on the drug properties and predictions are accurate for drugs with a low extraction ratio (ER) that bind to albumin and are hepatically cleared by an enzyme that is mature. For drugs that are excreted through glomerular filtration, predictions are accurate (PE within ±30% as compared to PBPK predictions) in children as young as one year of age for all drugs, except for drugs highly bound (i.e., adult unbound fraction in plasma ≤ 0.12) to α1-acid glycoprotein (AAG). Using PBPK principles, there is no evidence for one unique allometric exponent in paediatric patients, even in scenarios that consider size-related changes only. As PE is most sensitive to the allometric exponent, drug properties and maturation in the youngest children, AS0.75 leads to increasingly worse predictions with decreasing age.

In **chapter 4**, we evaluated the accuracy of linear scaling using the PBPK workflow developed in **chapter 3**, and for situations where linear scaling does not lead to accurate predictions, we compared the results with AS0.75. Currently there is renewed interest in linear

scaling because there seem to be only limited differences compared to commonly used AS0.75. We found that linear CLp scaling is accurate down to the age of 1 month for drugs undergoing glomerular filtration, except for drugs highly bound to AAG. For hepatically cleared drugs, linear scaling is reasonably accurate down the age of 2 years, except for AAG bound drugs with a low ER and isoenzyme activity similar to or higher than in adults. In neonates, linear scaling outperforms AS0.75 for drugs excreted through glomerular filtration, irrespective of whether they are bound to human serum albumin (HSA) or AAG. These results suggest that paediatric patients can in many cases be treated as small adults.

8.1.2. Scaling methods accounting for isoenzyme maturation for prediction of clearance in children

In **chapter 5**, we identified conditions for which extrapolations of population pharmacokinetic (PopPK) covariate models between drugs sharing an elimination pathway consistently lead to accurate pathway-specific CLp scaling from adults to children for drugs undergoing hepatic metabolism. This scaling approach has enabled accelerated development of paediatric models and dosing recommendations. For the purpose of this study, the PBPK simulation workflow utilizing mechanistic equations defining hepatic metabolism developed in the previous chapters was used. We found that drugs eliminated via the same pathway require similar paediatric dose adjustments only in a limited number of specific cases, depending on the ER of the drugs, unbound fraction, type of binding plasma protein, and the fraction metabolized by the isoenzyme pathway for which CLp is scaled. Overall, between-drug extrapolation of paediatric covariate functions for CLp is mostly applicable to low and intermediate ER drugs eliminated by one isoenzyme and binding to HSA in children older than 1 month.

In **chapter 6**, we evaluated currently used simple methods to scale clearance from adults to young children. To date, scaling from adults to children using allometric exponents that vary with age (age-dependent exponent (ADE)) and AS0.75 with isoenzyme maturation functions similar to those implemented in PBPK models (AS0.75+MF_{PBPK}) represent potentially valuable scaling methods, but an assessment of their applicability is lacking. The aim of this study was therefore to systematically assess the scaling accuracy of ADE and AS0.75+MF_{PBPK} in children younger than five years for drugs undergoing hepatic metabolism. This was performed using the previously developed PBPK-based simulation workflow

including hypothetical drugs with a wide range of properties and metabolized by different isoenzymes. In this platform, the impact of drug properties and isoenzyme maturation on clearance maturation and the accuracy of each scaling method was investigated to define scenarios for which these methods systematically lead to accurate paediatric CLp scaling. The drug properties that were most relevant in predicting the systematic accuracy of the scaling methods were the ER in adults and the type of plasma proteins bound (HSA or AAG). We found that these drug properties and isoenzyme maturation highly impact clearance maturation in all children younger than five years, leading to a wide range of paediatric clearance values, which ultimately prevents the systematic accuracy of scaling methods solely accounting for age and bodyweight such as ADE. In contrast, paediatric clearance for all low and intermediate ER drugs can be accurately scaled using AS0.75+MF_{PBPK} except for drugs binding to AAG in neonates. For other drugs, no simple scaling method is yet accurate.

8.1.3. Towards improved paediatric clearance predictions with the combined use of population PK and PBPK modelling approaches

In **chapter 7**, we developed 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 ($CLint_{u,WL}$) and hepatic blood flow (Qh) in children. Estimation of PBPK parameters using clinical data is highly relevant, since the parameters that are required for PBPK models that are essential in drug development, cannot always be directly measured. First, structural identifiability was enabled through re-parametrization and the definition of essential trial design components. Subsequently, requirements for the trial components to yield precise estimation of the PBPK parameters and their inter-individual variability were established using a novel application of population optimal design theory. Finally, the performance of the proposed trial design was assessed using stochastic simulation and estimation. The results show that precise estimation of $CLint_{u,WL}$ and Qh and their inter-individual variability requires a trial with two drugs, of which one has an ER ≤ 0.27 and the other has an ER ≥ 0.93. The proposed clinical trial design was found to lead to precise and accurate parameter estimates and was robust to parameter uncertainty. The proposed framework can be applied to other PBPK parameters and facilitate the development of PBPK models.

8.2. Conclusions and perspectives

8.2.1. Clearance scaling from adults to children: a decision tree

As described in **chapter 1**, accurate clearance scaling from adults to children is key to improve and expedite paediatric dose tailoring. Although PBPK models represent the most accurate scaling method available to date, their use requires specific expertise and data from various and complex *in vitro* or *in vivo* experiments, leading to a need for simpler but accurate scaling methods. Through **section II** and **section III**, we developed and applied a PBPK-based simulation workflow in order to define scenarios for which different simple scaling methods are systematically accurate. In **section II**, we investigated two scaling methods that solely use bodyweight as scaling variable, namely AS0.75 and linear scaling. In **section III**, we investigated scaling methods relying on more information, accounting for isoenzyme ontogeny and demographic measurements (i.e., bodyweight alone or together with age). These methods require the knowledge of not only demographic values of the population for which the predictions are performed, but also of the ontogeny of the eliminating enzymes of the investigated drug and the fraction metabolized in adults by each of the isoenzymes involved in drug clearance. Based on the applicability of these different investigated scaling methods, a clearance scaling decision tree is proposed in Figure 1, which allows for the first time (clinical) pharmacologists to select scaling method(s) that require a minimum but sufficient amount of information to accurately scale clearance according to the paediatric age range and properties of the drugs under investigation.

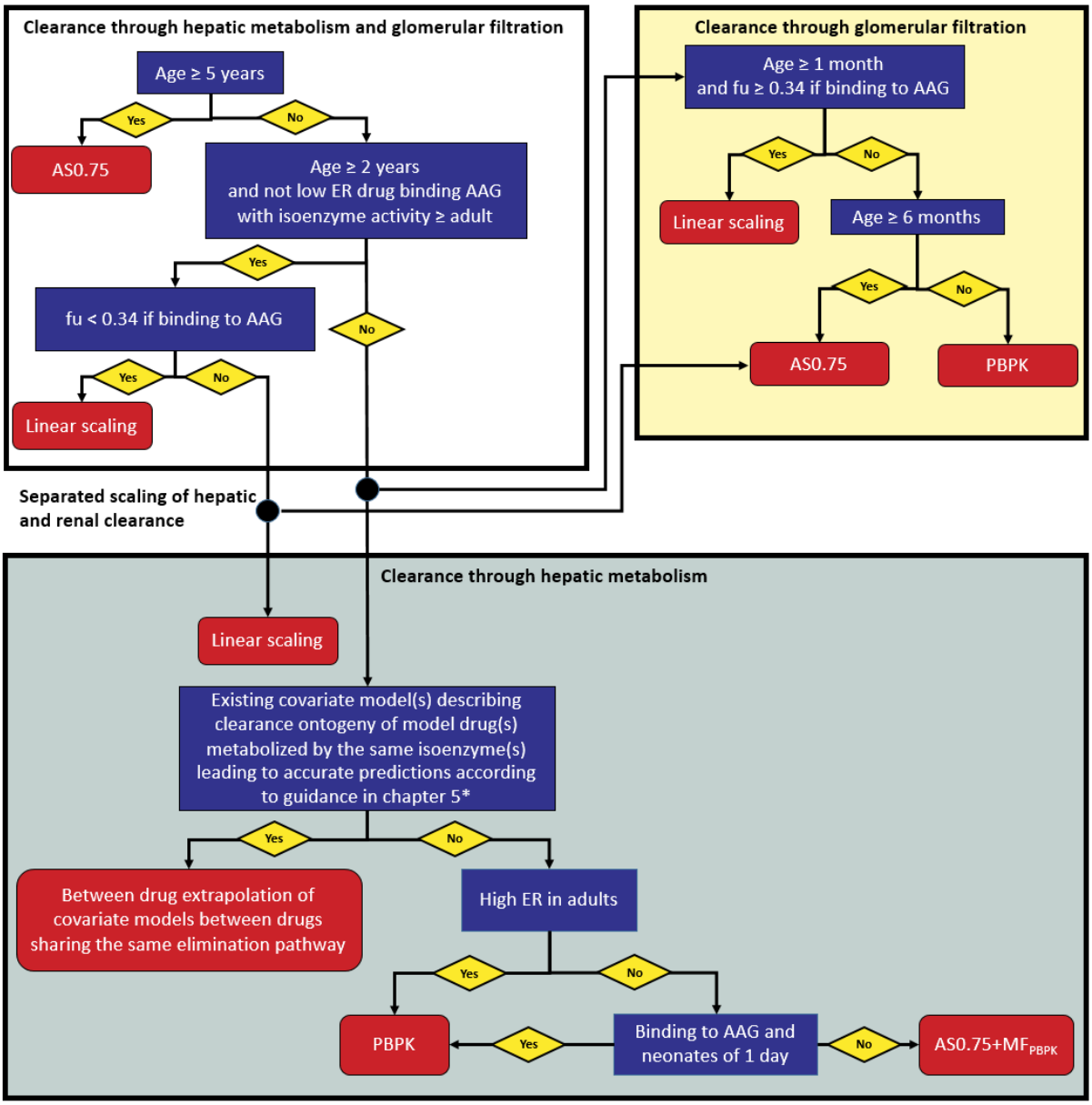


Figure 1 *Paediatric clearance scaling decision tree based on elimination pathway, drug properties and age. The white block indicates how to scale total drug clearance for drugs eliminated by hepatic metabolism and glomerular filtration. The yellow and grey blocks indicate how to scale either clearance due to glomerular filtration or due to hepatic metabolism respectively and need to be combined in case the situation of the white block does not apply. AS0.75; allometric scaling on the basis of bodyweight to the power of 0.75, PBPK: physiologically-based pharmacokinetic modelling, ER: extraction ratio in adults, AS0.75+MF$_{PBPK}$: fixed allometric exponent of 0.75 combined with functions similar to those implemented in physiologically-based pharmacokinetic (PBPK) models accounting for both isoenzyme and MPPGL maturation (**chapter 6**), AAG: α1-acid glycoprotein, fu: adult unbound drug fraction in plasma. * **Chapter 5** shows that between-drug extrapolation of paediatric covariate functions using this approach is mostly applicable to low and intermediate extraction ratio drugs eliminated by one isoenzyme and binding to human serum albumin in children older than 1 month, because its use is restricted by the degree of similarity of the fu and ER between the model and test drug, as well as the fraction of the model and test drug metabolized by the different isoenzymes. Supplementary material 2 and 3 of **chapter 5** presents model-test drug scenarios that for drugs binding to human serum albumin or the alpha-1 glycoprotein respectively, lead to accurate pathway specific plasma clearance predictions for a test drug after between-drug extrapolation of a pathway specific paediatric covariate function.*

The paediatric scaling decision tree in Figure 1 is composed of three blocks that contain scaling methods (red rectangles) and requirements for their accuracy (blue rectangles), each block corresponding to different drug elimination pathways that can be scaled with reasonable accuracy (±50% prediction error as compared to PBPK-based simulations) by the methods they contain. The use of scaling methods outside the defined requirements in the decision tree does not mean that scaled CLp values will be inaccurate, but that accuracy cannot *a priori* be guaranteed.

The white block indicates how to scale total clearance of drugs eliminated by hepatic metabolism and glomerular filtration. The yellow and grey blocks indicate how to scale either clearance due to glomerular filtration or due to hepatic metabolism respectively. For drugs undergoing both hepatic metabolism and glomerular filtration when requirements for total clearance scaling using a single method (white block) are not met, separate scaling of hepatic and renal clearance is required (grey and yellow blocks).

The different requirements for scaling accuracy in the decision tree are based on the paediatric age range for the predictions, the isoenzyme activity compared to adults (maturation), whether the drug binds to AAG, the adult unbound drug fraction in plasma (fu), and the adult ER.

Isoenzyme activity corresponds to the unbound intrinsic clearance per gram of microsomes expressed as percentage of adult values. While AAG, a plasma protein to which drugs can bind, can limit the applicability of the different scaling methods, the decision tree is also applicable to drugs not binding to plasma protein and to drugs binding to HSA. The fu and ER in the decision tree are respectively the unbound drug fraction in plasma and the extraction ratio, as defined in adults since the value of these parameters can change with age and is often solely known in adults. The unbound drug fraction in plasma can undergo elimination unlike the fraction bound to plasma proteins. ER reflects to which extent drug clearance is driven by hepatic blood flow and intrinsic clearance, with clearance of low ER drugs (ER $\leq$ 0.3) mainly driven by intrinsic clearance, clearance of high ER drugs (ER > 0.7) mainly driven by hepatic blood flow, and clearance of intermediate ER drugs (ER between 0.3 and 0.7) driven by both hepatic blood flow and intrinsic clearance. For extrapolation of covariate models between drugs sharing the same elimination pathway, **chapter 5** provides guidance on the requirements for accurate scaling with this method, which is based on a combination of the aforementioned drug properties (i.e., the ER of the model drug, the type of plasma protein bound (either HSA or AAG) and the difference in ER and fu between the model

drug and the test drug) and additionally also based on the isoenzyme pathways involved in the drug clearance (e.g., SULT1A1 and CYP1A2) as well as the fraction of the metabolic clearance due to each of these isoenzyme pathways.

As an example, to scale CLp from adults down to children as young as 1 month for a drug that has a low ER in adults, binds to AAG with an fu of 0.6 and undergoes both hepatic metabolism and glomerular filtration, AS0.75 can be used to scale total clearance down 5 years of age (white block). For younger children, metabolic clearance (the fraction of the total drug clearance due to hepatic metabolism) and glomerular filtration are separately scaled and added up in order to scale total CLp. Hepatic clearance (grey block), can be scaled using AS0.75+MF_{PBPK} or between drug extrapolation of covariate models provided the guidance of **chapter 5** *a priori* predicts accurate CLp prediction for that drug. The part of drug clearance due to glomerular filtration for that drug can be scaled using linear scaling (yellow block).

As shown in Figure 1, for drugs undergoing glomerular filtration (yellow block), linear scaling can be used in children as young as one month of age, except for drugs that are highly bound to AAG, with an fu in adults < 0.34. For these drugs highly bound to AAG, AS0.75 can be used but only in children no younger than 6 months of age.

Disregarding the drug properties and the routes of drug elimination (white block), CLp can be accurately scaled from adults to children of 5 years and older using AS0.75, which solely requires information on bodyweight. For hepatically cleared drugs, linear scaling is reasonably accurate down the age of 2 years, except for AAG bound drugs with a low ER and isoenzyme activity similar or superior to adult values (white block) and, if the drug also undergoes glomerular filtration, except for drugs highly bound to AAG for which separate scaling of hepatic (linear scaling in grey block) and renal clearance (AS0.75 in yellow block) is required.

For CLp scaling to younger children involving drugs undergoing hepatic metabolism the use of scaling methods accounting for isoenzyme ontogeny such as extrapolation of covariate models between drugs sharing the same elimination pathway (**chapter 5**) or AS0.75+MF_{PBPK} (**chapter 6**) is required (Figure 1, grey block). Indeed, the wide difference in maturation patterns between different isoenzymes in those very young ages leads to a wide variation in CLp ontogeny between drugs, which cannot be solely described based on demographic information, as found in **chapter 6**. However, the wide variation in clearance ontogeny across different drugs in young children is not solely due to isoenzyme maturation,

but also to other variables underlying drug clearance, impacting plasma clearance maturation in a drug-specific manner, such as the ER, type of plasma protein bound and maturation of its concentration. Therefore, the applicability of scaling methods accounting for isoenzyme maturation (i.e., AS0.75+MF$_{PBPK}$ in **chapter 6** and between drug extrapolation in **chapter 5**) is also dependent on the drug properties, and more specifically on the drug ER and type of plasma protein the drug binds to. As a result, the accuracy of these methods is mostly limited to low and intermediate ER drugs since clearance ontogeny of these drugs is mostly impacted by isoenzyme maturation. Additionally, for drugs binding to AAG in neonates, the steep maturation of AAG leads to a high impact of fu on clearance ontogeny, preventing the systematic accuracy or limit the applicability of these methods for these drugs.

To scale CLp using between drug extrapolation of covariate models, CLp through each isoenzyme pathway of the drug (test drug) is scaled from adults to children using a covariate model that describes CLp ontogeny of another drug (model drug) due to the respective isoenzyme pathway (**chapter 5**). This method is illustrated in Figure 2 for model and test drugs eliminated by one isoenzyme.

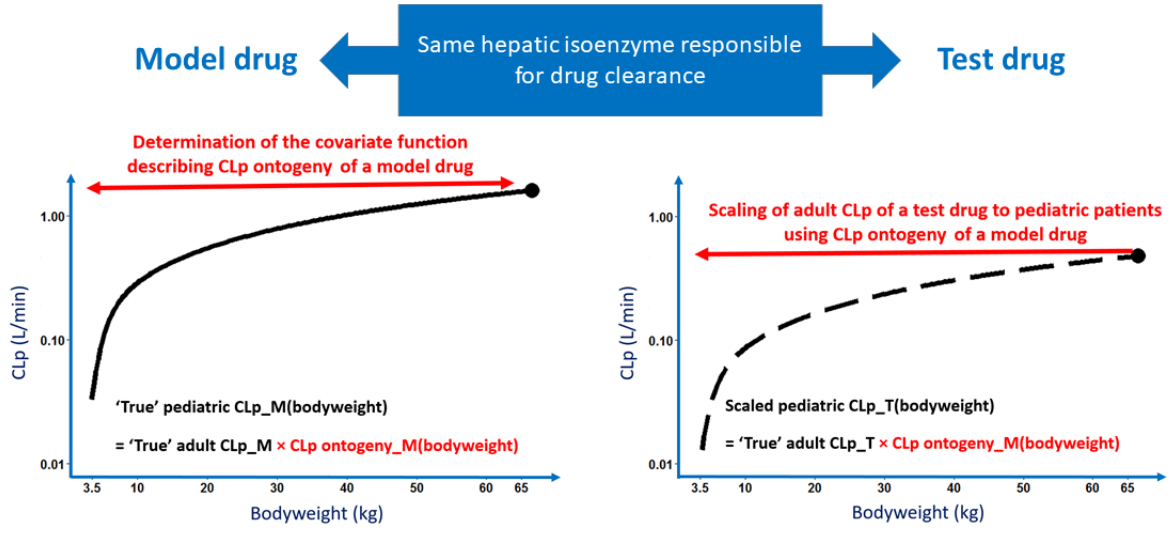


Figure 2 *Illustration of between-drug extrapolation of paediatric covariate functions to scale hepatic plasma clearance (CLp) from adults to paediatric patients for drugs eliminated by the same isoenzyme. The black dot in both graphs shows the adult hepatic CLp value for the model drug ('true' adult CLp_M) and the test drug ('true' adult CLp_T). The solid black line represents the change in CLp of the model drug throughout the paediatric age range, which is described by a paediatric covariate function based, in this example, on bodyweight (CLp ontogeny_M (bodyweight)). The dashed black line represents the scaled paediatric CLp predicted for the test drug by between-drug extrapolation of the paediatric covariate function obtained for the model drug (CLp ontogeny_M (bodyweight)). Figure taken from* ***chapter 5*** [3].

With this method, the scaling functions (i.e., covariate functions describing plasma clearance ontogeny of the model drugs) aggregate information not only on the ontogeny of the scaled isoenzyme pathways but also on drug properties and, in case of elimination through multiple pathways, on the ontogeny of other isoenzyme pathways responsible for the model drug elimination. Therefore, the applicability of this method is restricted by the degree of similarity of the fu and ER between the model and test drug, as well as the fraction of the model and test drug metabolized by the different isoenzymes. This method is mostly applicable to low and intermediate ER drugs that are mainly metabolized by one isoenzyme and binding to HSA in children older than one month. However, unlike AS0.75+MF_{PBPK}, this method can be applied to predict clearance of high ER drugs and drugs binding to AAG in neonates of one day, albeit in very specific cases. Scenarios where this method leads to accurate CLp predictions (defined as ±30% prediction error compared to PBPK simulations) can be found in supplementary materials 2 and 3 of **chapter 5**. An illustration of the use of this framework to '*predict*' whether between-drug extrapolation is possible to '*scale*' CLp for commonly used CYP3A substrates in children has been provided [submitted for publication [4]]. In this work, a maturation function derived from midazolam (model drug) was used to scale clearance across the entire paediatric age range or parts of this range for diverse CYP3A substrates (test drugs) for which the framework predicted accurate CLp scaling based on the ER, fu and the fraction of the drugs metabolized by CYP3A of both the model drug and test drugs. Alternatively, AS0.75+MF_{PBPK} (**chapter 6**) can be used for low (PE within ±30% compared to PBPK predictions) and intermediate ER drugs (PE within ±50% compared to PBPK predictions), except for drugs binding to AAG in neonates of one day. With this method, the maturation function(s), which are similar to those implemented in PBPK models, should account for isoenzyme maturation per gram of liver (e.g., both maturation in isoenzymes in microsomes and maturation in microsomal protein per gram of liver or MPPGL) for each isoenzyme involved in drug clearance. Indeed, isoenzyme maturation functions that do not take MPPGL maturation into account was found to lead to important prediction bias (**chapter 6**) and therefore should not be used when scaling clearance with AS0.75+MF_{PBPK}.

For drugs that have a high ER in adults, and for drugs binding to AAG in neonates of one day, either accurate scaling using extrapolation of covariate models between drugs sharing the same elimination pathway can be ensured *a priori* (see **chapter 5**), or no simple scaling method will be systematically accurate, and, as a result, clearance should be predicted using PBPK modelling approaches. It is emphasized here that, in young children, clearance of drugs

that have a high ER in adults, might not solely reflect hepatic blood flow like in adults, but also reflect isoenzyme activity. This is due to the change in ER in young children with isoenzyme maturation [5] that is often overlooked. Therefore, clearance ontogeny of these drugs reflects hepatic blood flow and isoenzyme activity to a different extent, depending on the isoenzyme maturation (with age) and the ER of these drugs in adults, ultimately leading to a wide variation in clearance ontogeny across drugs that have a high ER in adults (**chapter 6**). Because this shift in the contribution of hepatic blood flow to hepatic clearance is not accounted for in any of the scaling methods that are based on bodyweight and/or age only, even when accounting for isoenzyme ontogeny, their accuracy is hindered for these drugs.

8.2.2. The paediatric clearance scaling decision tree in practice

By unravelling the minimum amount of information required for accurate scaling of clearance from adults to children of various ages, the paediatric decision tree (Figure 1) enables the selection of the simplest scaling methods that can be used instead of PBPK models, thereby decreasing computational efforts and required information collection. Scaling methods selected based on this decision tree can be used in order to optimize paediatric clinical trials through the definition of the paediatric dosing regimen(s), informative sampling times [6], and inclusion criteria based on the scaling variables [7], to ensure accurate and precise PK parameter estimates. Additionally, these scaling methods can be implemented as priors during population PK analysis in order to inform the analysis of underpowered PK studies, such as for some specific diseases for which only small numbers of paediatric patients can be enrolled.

In children of 5 years and older, only adult clearance values and bodyweight of the paediatric patients are needed for accurate clearance scaling using AS0.75, with an absolute prediction error of less than 50%, and when isoenzymes are mature, of less than 30%. This information might also be sufficient to scale clearance with reasonable accuracy (PE within ±50%) in children as young as 2 years or one month of age using linear scaling for drugs undergoing hepatic metabolism or glomerular filtration respectively. However, this will require knowledge of the type of plasma protein bound and, for drugs undergoing hepatic metabolism binding to AAG, of the ER, fu and the maturity of the isoenzymes involved in drug clearance, since applicability of linear scaling depends on these parameters in children between 2 and 5 years of age (Figure 1). Similar for drugs undergoing glomerular filtration, linear scaling for instance only applies down to one month of age if the drug does not bind to

AAG with an fu ≥ 0.34. For hepatically cleared drugs which are the main focus of this thesis, in younger children, while the proposed scaling methods require less information on drug- and system-specific properties compared to PBPK models, they require, similarly as for PBPK models, accurate estimates of the fraction of the drug metabolized in adults and the availability of maturation functions or covariate models for each isoenzymes involved in the drug clearance (see **chapter 5** and **chapter 6**).

The fraction of drug metabolized by diverse isoenzymes is often available from adult ADME (Absorption Distribution Metabolism Excretion) studies, but might not be available for old drugs due for instance to lack of specificity, sensitivity and efficiency of quantitative analytical methods [8,9], a lack of method selectivity for metabolic route qualification [10,11] or unawareness of pharmacokinetic differences between enantiomers (stereo selectivity in drug metabolism) [12,13]. In case this information is missing, it could be collected in children older than 5 years, for which accurate scaling solely requires bodyweight measurements, and then used to support accurate scaling of clearance in younger children. This necessitates the conduct of a mass balance study, which may require the collection of urines, faeces in addition to blood samples. However, this type of study is feasible in children of that age.

When information on isoenzyme maturation for part of the isoenzymes involved in drug clearance is missing, the lowest reported isoenzyme maturation value in the different age groups could be used instead, which would favour under-predictions over potential over-predictions of clearance, thereby reducing risk of adverse events.

For drugs undergoing both hepatic metabolic clearance and glomerular filtration, in young children each route of elimination can be scaled using the paediatric decision tree (i.e., combination of information in the grey block with information in the yellow block), since glomerular filtration does not impact hepatic metabolic clearance nor its ontogeny. For these drugs, additional information on the fraction of the drug eliminated through glomerular filtration in adults is required so as to separately scale hepatic metabolic clearance and renal clearance.

For drugs that are transporter substrates, bind to lipoproteins and for situations where clearance ontogeny might be impacted by disease or drug effect, the paediatric decision tree might not hold true, since these situations were not considered in this thesis due to a lack of available information to implement in PBPK models. In those cases, valuable alternatives could be microdosing studies [14,15], or adaptive design studies [16] with first a sub-therapeutic

dose. This first dose can be predicted taking the minimum dose predicted using PBPK models with inferences on the processes for which data are currently lacking (e.g., transporter ontogeny, impact of disease on physiological parameters, etc) and applying a safety factor as performed in adults [17].

8.2.3. The paediatric clearance scaling decision tree: future development

Although the paediatric decision tree allows for the identification of clearance scaling methods for a wide range of drugs, further investigations are needed for paediatric sub-populations and drugs subject to or driving processes potentially impacting clearance that were not investigated in this thesis. In many cases, this would first require the quantification of these processes and/or of system-specific parameters of these populations before they can be implemented in PBPK models, since they are currently poorly characterized. This is for instance the case of preterm neonates [18], for which drug clearance is known to potentially differ from term neonates, drugs that are transporter substrate [19] and renally cleared drugs undergoing active tubular absorption and/or secretion. Once sufficient data (e.g., on transporters abundance in the liver, in the renal tubules or reabsorption) across the paediatric age range has been collected, implemented and validated in PBPK models, the impact of these processes could be investigated using a PBPK simulation workflow similarly as in **section II** and **III**.

For some diseases and/or drugs, physiological parameters which drive drug clearance and/or relationship between demographic values and clearance ontogeny can be altered, either directly or through drug-drug interaction. For instance, plasma protein binding can be reduced due to uraemia, hypoalbuminemia or drug-drug interaction, which can significantly alter clearance of drugs with high protein binding and low ER or undergoing glomerular filtration [20–22]. Another example is obese children, for which clearance ontogeny as well as its relationship with total bodyweight are likely to differ from patients with normal weight [23,24]. Therefore, the relevant system-specific parameters for these paediatric sub-populations that have already been characterized could be implemented in the PBPK simulation workflows developed in this thesis in order to assess whether and how the decision tree in Figure 1 should be adapted.

Mechanistic characterization of some of the scenarios that were not investigated in this thesis has already been recognized as important and is currently under research, such as for

active drug transporters [25–27], pre-term neonates [18] and obese children [23,24]. However, the relevance of the mechanistic characterization for other scenarios remains unclear. Discrepancies between CLp ontogeny as quantified based on paediatric clinical data and the scaled CLp using the relevant method defined in the decision tree could help to pinpoint specific scenarios for which such investigations are highly relevant.

While accurate scaling of clearance from adults to paediatric patients is of utmost importance to define first-in-child doses and plan informative sampling times and patient recruitment for paediatric clinical trials, accurate prediction of the drug absorption rate and bioavailability can also be crucial when the drug is administered through extra vascular routes. Ontogeny in drug bioavailability will impact the dose to be administered to reach the target exposure in paediatric patients. In case drug peak concentrations drive drug toxicity and/or efficacy and in case of slower absorption rate than elimination rate, the ontogeny in the drug absorption rate should be accurately predicted to ensure efficacious and safe dose tailoring. This also applies to estimation of volume of distribution in children which may be of relevance for instance for drugs given intravenously and where peak concentrations determine the effect like anaesthetics or muscle relaxants and for drugs with a prolonged half-life in order to determine a loading dose.

8.2.4. The use of popPBPK modelling to extend predictions to subpopulations

PBPK models are instrumental in understanding and predicting PK of diverse drugs but require for their development extensive data collection of *in vitro*, *ex vivo* and/or *in vivo* measurements, which are not always accurate, or hypotheses on system-specific parameters that are not directly measurable, such as hepatic blood flow in paediatric sub-populations such as (preterm) neonates. Therefore, time consuming iterative learn and confirm cycles are needed for the validation of these models. Direct estimation of PBPK parameters based on clinical data has the potential to overcome some of these problems and may represent a valuable method to expedite the development of PBPK models for different understudied sub-populations, such as preterm neonates or obese children and adults, or understudied PK processes, such as first pass metabolism. Moreover, this method has been found superior to *in vitro* estimation. For instance it has been shown that isoenzyme maturation functions developed based on clinical data perform markedly better than those developed based on *in vitro* data [28,29]. Since system-specific parameters are often structurally non-identifiable, that is

to say not all parameters can be estimated from the available data, currently some of the model parameters are fixed to measured values, usually those that can be accurately and directly measured. This is however problematic when the parameters that should be fixed cannot be accurately measured, as bias in their measurement is likely to lead to bias in the estimated parameter(s). Alternatively, one can develop (semi-)physiological covariate models for model drugs that describe clearance ontogeny via a specific pathway, thereby characterizing the overall influence of system- and drug- specific parameters on the process described. Such work has been performed for the characterisation of first-pass metabolism in preterm neonates [30] or clearance ontogeny in obese patients driven by CYP3A using CYP3A probe drugs [31]. Whereas this method allows to accurately predict processes of other drugs undergoing the same processes, we found in **chapter 5** that it can be limited to situations where some drug properties of the model drug (drug for which the process has been described) and the test drug (drug for which predictions are performed) are similar.

Therefore, new methodologies are needed to overcome structural identifiability problems of PBPK models in order to allow for the accurate and precise estimation of all system specific parameters. Indeed, being able to identify PBPK parameters that cannot be obtained by direct experimental measurements in a time and cost-efficient manner would greatly improve and expedite the development of PBPK models and their predictive performance, without putting too great a burden on the population involved. To this end, we proposed in **chapter 7** of this thesis a new 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 this chapter, the use of clinical data of different drugs with specific properties enables the identification of parameters that are unidentifiable based on data of one drug. Moreover, using popPK for parameter estimation enables the estimation of the parameter value in the studied population as well as its variability. The results show that trial requirements to perform such analysis are difficult to meet, with a high number of patients and drugs with very specific properties needed. This highlights the importance of assessing the clinical trial design requirements before conducting clinical trials or gathering information for a meta-analysis when aiming at estimating PBPK parameters based on clinical data. Defining *a priori* clinical trial requirements enables to assess the feasibility of the analysis and, when possible, to only select drugs whose PK profile is informative enough for such studies.

Although in **chapter 7** the proposed method is illustrated with the estimation of hepatic blood flow and whole blood intrinsic clearance in paediatric patients and adults, it could be used to estimate the same or other key PBPK parameters in different sub-populations, such as critically ill or obese patients of various ages or even in different species. To apply this method to a different population (or specie), similar as in the example given in **chapter 7**, a range of likely values for each of the system specific parameters of the PBPK model that are to be estimated should be tested. For the application of this method to a different set of parameters, structural identifiability based on the simultaneous analysis of different drug should be ensured, which might require model re-parametrization, as illustrated in **chapter 7**, and/or additional clinical samples. This could be the case for instance of PBPK parameters describing first pass metabolism which is responsible for drug metabolism in the gastro-intestinal tract before the drug can reach the blood stream. Particularly in specific populations, it may be of relevance to understand the changes in first pass metabolism of drugs [32]. An often used PBPK model for first pass metabolism is the Qgut model, which is parametrized with both enterocytic blood flow and permeability clearance [33]. To allow for structural identifiability of these parameters, reparameterization can be done as described in **chapter 7**, but additionally, both iv and oral data of the parent compound and metabolites would be required. Indeed, while in **chapter 7** hepatic clearance is identifiable based on clinical data of drugs administered through a unique route (provided there is no flip flop phenomenon), first-pass metabolism requires the above-mentioned PK data to ensure its identifiability, which would require a cross over study or micro tracer study design.

As found in **chapter 7**, PBPK parameters that are unidentifiable based on the data of one drug can be simultaneously estimated based on clinical PK data of diverse specific drugs and a number of patients that is higher than that of classical non-mechanistic population PK analysis studies. Because of these specific requirements, the use of the analysis framework proposed in this chapter or similar approach, is crucial in order to identify *a priori* the feasibility and the requirements of clinical trials for such an approach, thereby guiding data collection for meta-analysis and/or the design of new clinical trials. Meeting these requirements will likely involve data sharing, which might be a major drawback of this approach given the current efforts that need to be made before data can actually be shared. In light of the need of clinical data from diverse drugs to improve PK predictions for first-in-child doses, and other understudied populations and improve the understanding of mechanisms impacting drug PK, failure in sharing data appears unethical, which questions current

regulations on data ownership. Currently, the importance of data sharing is more and more recognized, and data sharing projects have been developed in order to improve mechanistic understanding and quantitative modelling of drugs PK [34]. Examples of data sharing projects are the OrBiTo IMI project that is designed to improve the understanding and modelling of how drugs are absorbed [35] or the mechanism-based PK-PD modelling platform of TI pharma which aimed at the development of novel mechanism-based PK-PD modelling concepts for stationary and non-stationary biological systems [36].

8.2.5. Good modelling practice for the description of clearance ontogeny

In case data of children of different ages are available for analysis, the simplest covariate model, which solely relies on bodyweight as covariate, is allometric scaling with an estimated allometric exponent. Unlike theoretical allometry which aims at only accounting for size-related changes in clearance, the allometric equation with estimation of the exponent captures overall clearance ontogeny, accounting for both size- and age-related changes since bodyweight and age are highly correlated in children. Often, the estimated allometric exponent is confused with the theory-based exponent which only aims at scaling size-related changes in clearance, and values differing from 0.75 are misinterpreted as erroneous and as allegedly due to bias in the estimate of the allometric exponent arising from unpowered studies. For instance, it has been erroneously claimed that the confidence interval of the allometric exponent estimate should always include the value of 0.75 [37]. In **chapter 3**, we showed that the use of an exponent of 0.75 (AS0.75, the claimed theoretical allometric exponent) in order to predict overall clearance ontogeny can lead to highly biased predictions in children younger than 5 years (scenario 2 of **chapter 3**). In **chapter 6**, we found that values of the estimated exponent (accounting for both size- and age-related changes) can widely differ from 0.75 in children younger than 5 years, ranging from 0.57 to 2.06 for drugs undergoing hepatic metabolism, and varies with age, drug properties and the elimination pathway. Values found in that range are realistic, since these values were derived from PBPK knowledge and a similar range in the allometric exponent have been reported in popPK data analyses [38–41]. This wide range of estimated exponents reported in literature does not arise from estimation bias, as recently shown by Sinha *et al.* [42]. In this paper, the authors showed that 20 patients (from 3 years old up to adults), which is less than the number included in typical clinical studies, is sufficient to reach a study power of 80% or more, which is the power required for unbiased estimates of

the allometric exponent, even in case of high PK variability. Moreover, other values outside the range found in **chapter 6** could be expected when adult data is not included, since the allometric exponent depends on the age range studied, or in situations that have not been studied yet (e.g., drug transport).

Therefore, in order to estimate paediatric clearance in children younger than 5 years, in our opinion the allometric exponent should be estimated and not fixed to 0.75, and values differing from 0.75 should not *a priori* be interpreted as clinically implausible. In cases where the number of patients is small (< 20), which could for instance be the case for rare diseases, the study power to obtain an unbiased estimate of the allometric exponent is likely to be smaller than 80% and bias in the estimate might arise. In such situation one should consider fixing the covariate model parameters describing clearance ontogeny. If the allometric exponent estimate is however uncertain, then prior knowledge of clearance ontogeny would be required. While using a fixed allometric exponent of 0.75 is a reasonable approach for children of 5 years and older, as shown in **chapter 3** of this thesis, other scaling functions, e.g., linear scaling, should be selected in younger children, for which the paediatric clearance scaling decision tree can be used. This does not mean that AS0.75 cannot be accurate in children younger than 5 years, but it reflects that accuracy cannot be guaranteed in that age range since AS0.75 can lead to important bias in clearance predictions depending on the age and drug properties.

8.2.5.1. Assessing the bias and precision of the allometric exponent

The assessment of the bias and precision of the allometric exponent estimate is often poorly performed. Difference in sensitivity of the accuracy of clearance ontogeny predictions to the bias in allometric exponent has been shown in **chapter 3**. Indeed, in this chapter, we found that the younger the child, the more clearance predictions are sensitive to the bias in the bodyweight-based exponent. This means that the same difference between the true allometric exponent and the chosen fixed allometric exponent used to scale clearance can lead to a variety of differences in clearance prediction bias in different ages. This bias increases with decreasing age, which is further illustrated in Figure 3, where the changes in bias of the allometric exponent (exponent used for the predictions minus true exponent) with bodyweight (BW) leading to ±30% or ±50% prediction error in clearance (CLp PE) is displayed for scenarios where clearance is scaled from adult values and a median adult bodyweight of 70kg (see

equation 1). This figure shows that for younger children (lower bodyweights), to reach the same clearance prediction bias as in older children, the bias in allometric exponent should be much lower.

$$\text{Exponent bias (prediction – true)} = \frac{\log(\text{CLp PE} + 1)}{\log(\frac{\text{BW}}{70})} \quad (1)$$

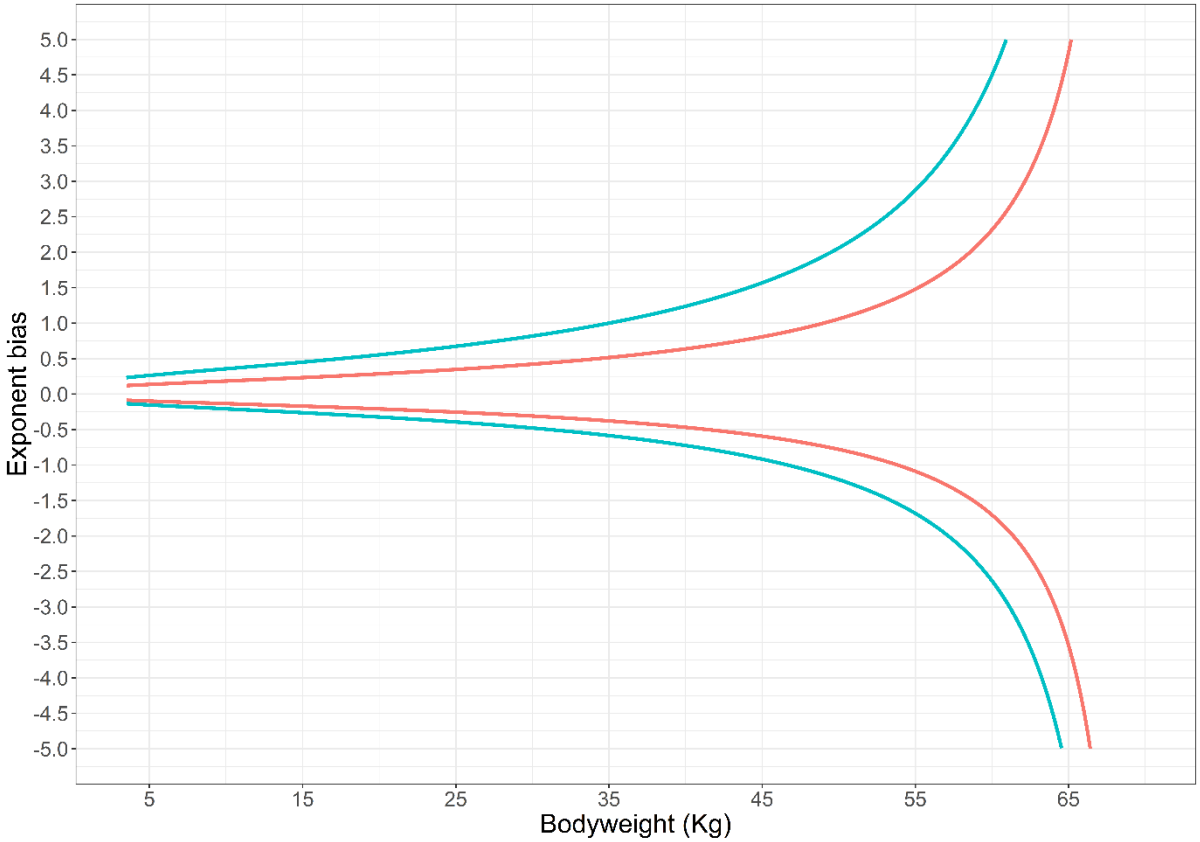


Figure 3 *Exponent bias (equation 1) leading to ±30% (red) or to ±50% (green) clearance prediction error versus bodyweight*

Since the aim of estimating the allometric exponent during clinical PK data analysis is not to estimate the exact true exponent, but to estimate an exponent that allows for accurate clearance predictions, bias in the allometric exponent should be assessed based on its impact on clearance accuracy. However, often the bias or uncertainty in the allometric exponent estimate is assessed based on fixed criteria, such as an accepted percentage of parameter bias or uncertainty. This is an important aspect that needs attention when finalising a (covariate) model together with standard model evaluation methods [43].

Although the allometric exponent was found to vary with age, drug properties and isoenzyme maturation in our PBPK-based simulation platform (**chapter 6**), this does not mean that a single allometric exponent cannot describe clearance ontogeny for a specific drug across a specific paediatric age range. Indeed, as shown in Figure 3, in the oldest children, clearance predictions are not sensitive to bias in the allometric exponent, and therefore one single exponent can accurately scale clearance across that paediatric age range. This also can be the case in younger children when changes in clearance with bodyweight follows the allometric equation, which is the case when the combination of the drug properties and maturation of isoenzymes involved in drug clearance leads to similar allometric exponents in that age range. When the variations in the allometric exponent across the studied age range are greater than the bias in allometric exponent leading to acceptable bias in clearance (see Figure 3) , more flexible functions should be used to capture clearance ontogeny, such as a bodyweight-dependent exponent [39,40].

8.3. Conclusion

Throughout this thesis, we developed a PBPK-based simulation workflow allowing to unravel the conditions for accurate scaling of drug clearance from adults to children as young as term neonates of one day for diverse methods. Based on these results, we proposed a clearance scaling decision tree, which allows for the first time (clinical) pharmacologists to select scaling method(s) that require a minimum but still sufficient amount of information to accurately scale clearance according to the paediatric age range and properties of the drugs under investigation. Moreover, the PBPK-based simulation workflow provides a mechanistic understanding of the diverse challenges in scaling drug clearance, as for instance the steep maturation of AAG in young children or the changes in ER with age due to isoenzyme maturation, which hinders the accuracy of most clearance scaling methods for drugs binding to AAG and for high ER drugs respectively. Moreover, we provided an analysis framework to assess the feasibility and clinical trial requirements for the estimation of PBPK parameters using population pharmacokinetic modelling (popPBPK), which has the potential to expedite development of PBPK models for understudied paediatric subpopulations. Such framework is crucial to guide clinical trial design or data collection for meta-analysis, as we found that trial requirements to perform popPBPK modelling are difficult to meet, as a high number of patients and drugs with very specific properties are needed. Finally, we broke through the beliefs and

misconceptions around allometric scaling using a bodyweight-based exponential relationship with a fixed exponent of 0.75, showing that there is no universal allometric exponent to scale size-related changes in clearance across the paediatric age range and providing good modelling practice for the estimation of the allometric exponent to scale both size- and age-related changes in clearance.

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