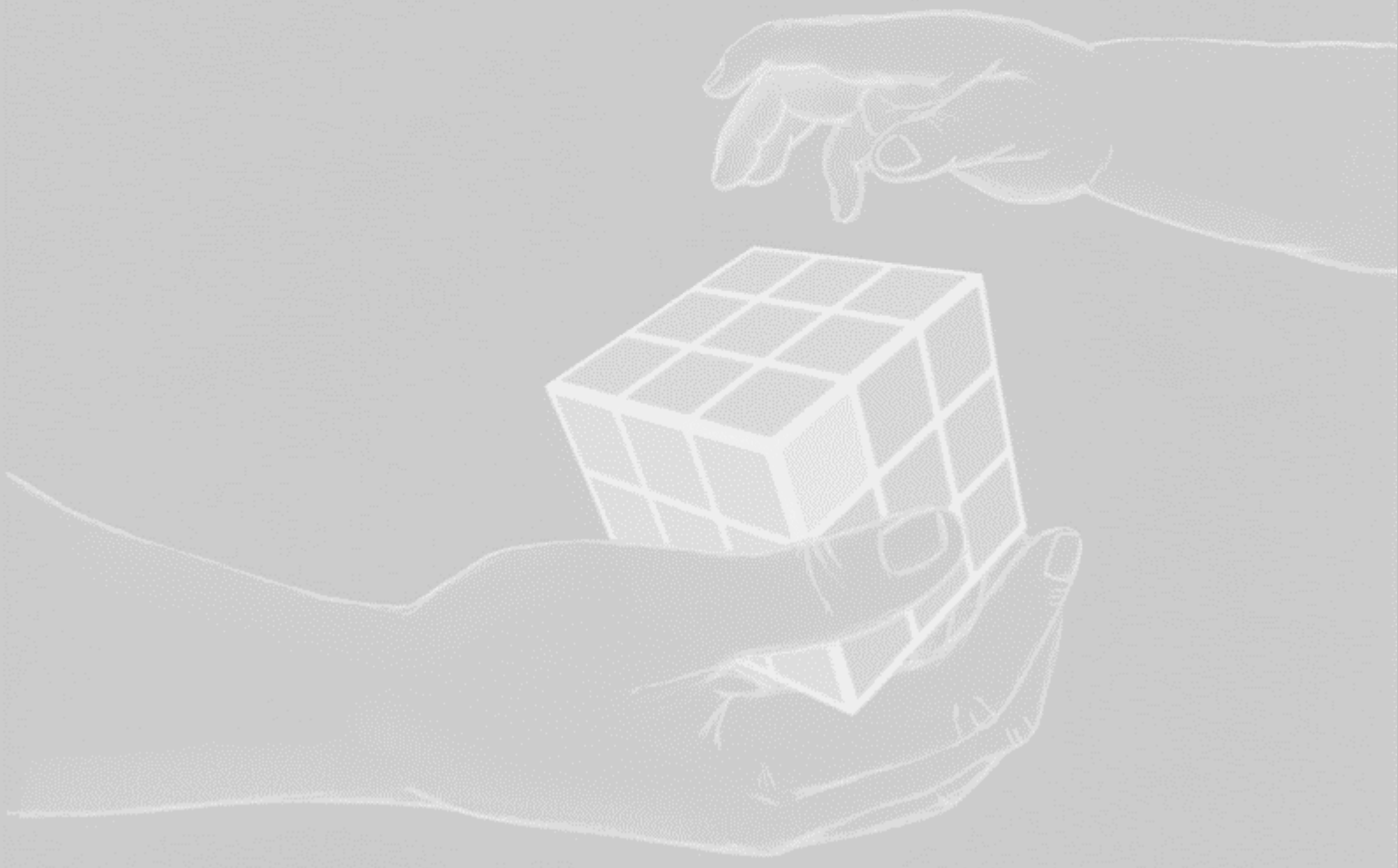
How to scale clearance from adults to children for drugs undergoing hepatic metabolism? Insights from advanced PBPK modelling and simulation

Calvier, E.A.M.

Chapter 1

General introduction



While in adult patients clinical trials have long been considered mandatory in order to ensure safe and efficacious drug treatment, they have long been thought unethical in paediatric patients [1]. Additionally, paediatric drug evaluation has often been neglected due to the diversity of challenges in performing pharmacological studies in paediatrics. These challenges include practical, ethical and economical concerns as well as challenges stemming from the major physiological changes taking place over the life spam of children [2]. This has led to the observed high paediatric unlicensed and off-label prescription rate, the latter being largely due to a lack of information on the recommended dosage [3–6]. Unlicensed drug prescription is the prescription of a drug that does not have a license, as for instance modified formulations, extemporaneous preparations or imported medicines. Off-label prescription is a prescription made outside the terms indicated in the product license, as for instance off-label use with regard to dose, age group, route of administration, or different indication [3].

To date there is agreement that off-label and unlicensed use of drugs is itself a suboptimal and at times potentially unethical situation that must be addressed [2]. In face of the urgent need to ensure safe and efficacious drug dosing in children for new drugs, but also currently available drugs, efforts have focussed on the advancement of dedicated paediatric clinical trials for each of these drugs across the paediatric age range.

Paediatric clinical trials enable the estimation of changes in clearance across the paediatric population, a key parameter for safe and efficacious paediatric dose tailoring. Characterizing clearance in paediatrics is challenging because this parameter varies across the paediatric population due to ontogenic processes and because few samples per patients and few patients per age group are available. Model-based approaches such as population modelling are necessary to overcome these challenges and enable the characterization of clearance ontogeny [7,8]. In addition, tremendous efforts have been made to accurately predict clearance ontogeny in children in order to derive individualized paediatric dosing regimen based on adult data and to integrate and maximize information throughout paediatric drug development, for which physiologically-based pharmacokinetic modelling (PBPK) approaches have been instrumental [9–12]. Such modelling and scaling methods are essential to overcome the problems related to the data analysis of underpowered studies and/or the lack of clinical data. Gaining a mechanistic insight into clearance ontogeny enables a rational choice of appropriate clearance scaling methods for their use throughout paediatric drug development and in clinical practice and could steer efforts of future research in this field.

1.1 Clearance: a key parameter for efficacious drug dosing

Pharmacokinetics is the study of the fate of substances in an organism, which involves four processes, namely absorption, distribution, metabolism and excretion (ADME) [13]. Pharmacokinetic (PK) studies are an important part of drug development, ultimately aiming at ensuring safe and efficacious drug treatment. Pharmacokinetic processes are described by pharmacokinetic parameters, such as clearance. Clearance describes the elimination of a substance, which may be due to both metabolism and excretion. This pharmacokinetic parameter is expressed as the volume of plasma or blood from which a compound is completely removed per unit of time and is a key parameter for efficacious and safe dose tailoring. Indeed, clearance, together with the administered dose and bioavailability for non-intravenous administration, drives the drug exposure which in turn, drives the drug effect and toxicity [14–16].

According to the paediatric study decision tree of the Food and Drug administration which has also been proposed in Europe (Figure 1) [17,18], PK studies should be systematically conducted in order to establish paediatric dosing so as to achieve a target concentration. This target concentration is the required drug concentration to achieve the desired effect and is derived based on exposure-response relationship. When disease progression and exposure-response relationship are expected to be the same as in adults, no pharmacodynamics (PD) studies are undertaken and the target concentration is taken to be the same as in adults (option C in the paediatric decision tree). When differences in disease progression and/or exposure-response relationship are expected compared to adults, these differences are assessed through the conduct of PK/PD or efficacy trials in order to define the target concentration in paediatric patients [19]. While classically randomized placebo controlled trials are performed for PK/PD and efficacy studies, the use of a placebo arm is sometimes unethical in paediatric patients and therefore in these cases, comparative effectiveness or non-inferiority designs are the preferred approach [20].

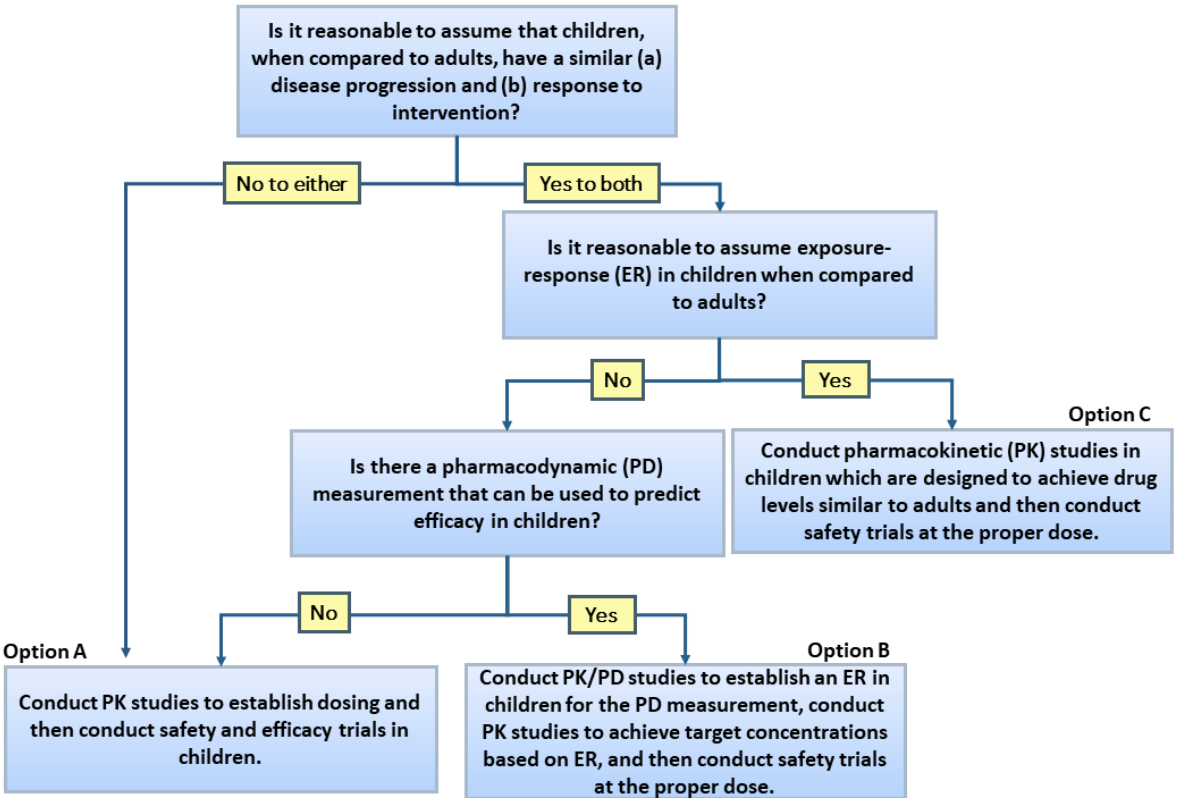


Figure 1 *FDA paediatric study decision tree* [18]

1.2 Clearance across the paediatric population: a moving target

Clearance of a drug, as other PK parameters, is driven by complex interactions between system-specific parameters, which are represented by anatomical and physiological measures, and drug-specific parameters. This is for instance reflected in different PK profiles of drugs with different drug properties. An illustration of the relationship between system- and drug-specific parameters on paediatric clearance of drugs undergoing hepatic metabolism is given in Figure 2. Relevant parameters to mechanistically describe clearance of such drugs are hepatic blood flow (Qh), the unbound drug fraction in plasma (fu), the blood to plasma ratio (B:P), and the intrinsic metabolic clearance in the liver based on unbound drug concentration (CLint). Qh and for instance isoenzyme abundance are purely system-specific parameters, whereas fu, B:P, and CLint are derived from both physiological and drug-specific parameters (Figure 2).

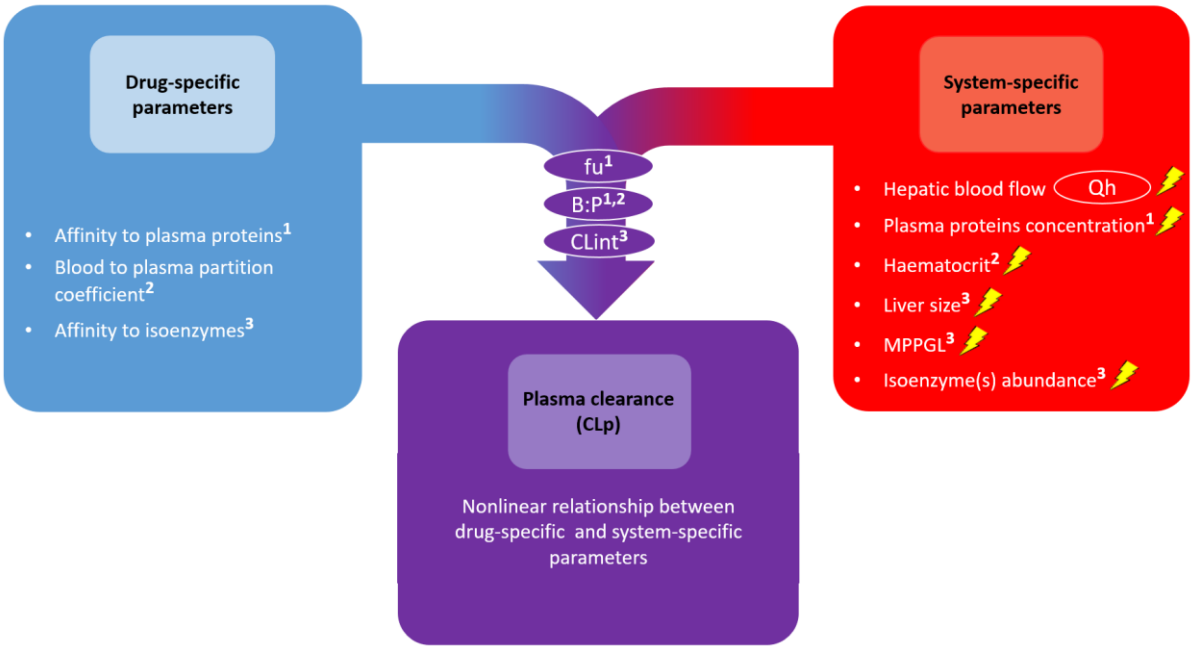


Figure 2 *Schematic representation of the relationship between drug-specific and system-specific parameters driving hepatic plasma clearance (CLp). Parameters within circles are directly used in the physiologically based pharmacokinetic hepatic clearance model (e.g., dispersion model). Parameters in the purple circles represent composite parameters that are derived from the system-specific parameters and the drug-specific parameters indicated by the numbers in the superscripts. In children, each of the system-specific parameters change with age, each represented by a lightning bolt. B:P, blood to plasma ratio; CLint, intrinsic metabolic clearance in the liver based on unbound drug concentrations; fu, unbound drug fraction in plasma; MPPGL, microsomal protein per gram of liver. Figure taken from Calvier et al.* [21].

From birth to adulthood, children undergo physiological changes due to ontogenic (or maturational) processes in system-specific parameters, which are highlighted by lightning bolts in Figure 2. The ontogeny of each of these system-specific parameters has their own profile. Figure 3 for instance shows ontogeny profiles of some of these system-specific parameters as relative values to the corresponding adult level. Ontogeny in system-specific parameters drives clearance ontogeny in a drug-dependent manner due to the interaction between system-specific and drug-specific parameters. Indeed, clearance ontogeny depends on the drug elimination pathway and drug properties, as illustrated in Figure 3. Panel A of this figure shows the ontogeny in system-specific parameters impacting clearance of all drugs undergoing hepatic metabolism, while panel B shows the ontogeny of system-specific parameters solely impacting drugs with specific properties and eliminated by specific isoenzymes. For instance, on one hand, ontogeny in liver volume impacts clearance ontogeny

of all drugs undergoing hepatic metabolism. On the other hand, albumin ontogeny only impacts clearance ontogeny of drugs binding to albumin, and ontogeny in CYP1A2 only impacts clearance ontogeny of drugs eliminated (completely or partially) by this isoenzyme. This impact of ontogenic processes on the pharmacokinetics of drugs has been extensively reviewed in the literature [22–27], as it is responsible for the high pharmacokinetic variability between drugs and different paediatric ages that is observed in paediatric patients.

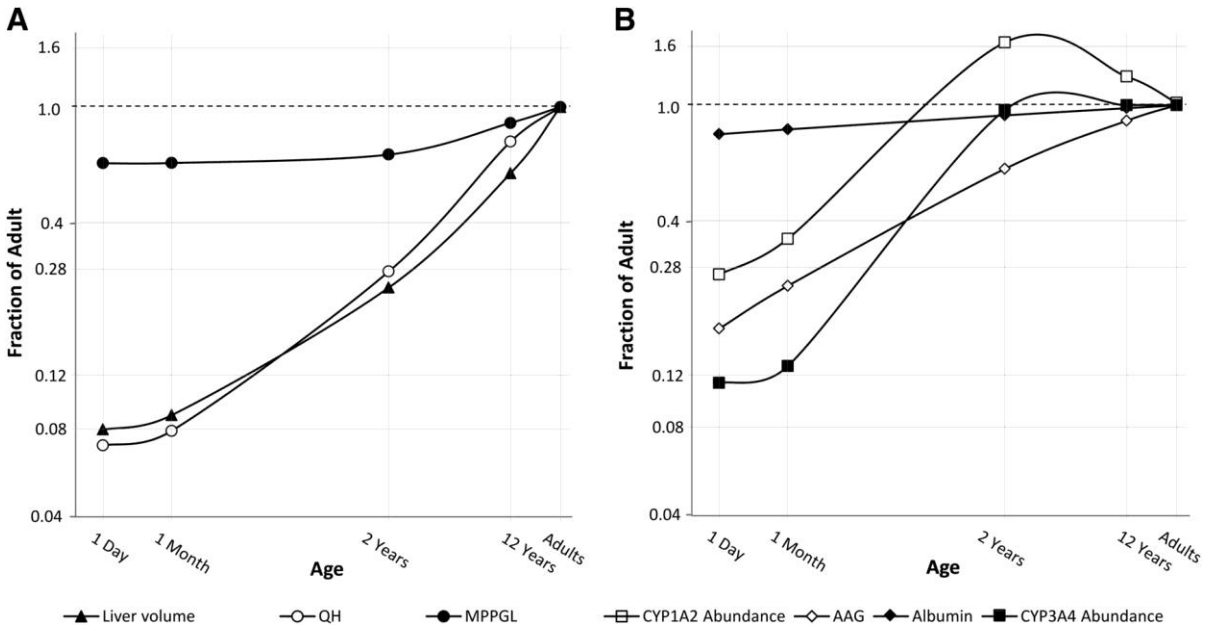


Figure 3 *Age-related variations in parameters defining clearance are shown as relative values to the corresponding adult level of each parameter, taken from Salem et al.* [28]*. (A) Changes in liver volume* [29]*, hepatic blood flow (Qh)* [30]*, and amount of microsomal protein per gram of liver (MPPGL)* [31] *that impact clearance of all drugs. (B) Relative values of serum albumin* [22,32,33]*, CYP3A4 abundance* [34] *alongside age variation in serum alpha-acid glycoprotein (AAG)* [32,33]*, and abundance of CYP1A2* [34]*, that impact clearance in a drug-dependent manner. The impact of the parameters shown in B will depend on the relative importance of the protein binding to each protein and the role of the specific enzyme to overall elimination.*

Additionally, transporters can also have a significant impact on clearance ontogeny but this impact is currently poorly characterized and hence often not considered [35–37]. Because clearance is a moving target across different drugs and different paediatric ages, quantifying its ontogenetic changes for each drug is of utmost importance for paediatric dose tailoring so as to achieve the required exposure in all paediatric patients.

1.3 Quantification of clearance ontogeny across the paediatric age range on the basis of paediatric clinical data

Clearance ontogeny should be accounted for in paediatric dose individualization in order to prevent variability in drug exposure across the paediatric age range. This requires the precise and accurate quantification of clearance ontogeny, which can be achieved through population pharmacokinetic modelling of paediatric clinical data. This model-based approach is recommended in paediatrics by the EMA [38,39] and FDA [40,41] because it can handle opportunistic, and limited blood samples sometimes available in children and, through covariate model building, allows for the quantification and explanation of the large inter-individual variability in pharmacokinetic parameters which is characteristic of the paediatric population [7,8].

Population pharmacokinetic models enable the estimation of individual pharmacokinetic parameters, as described in equation 1 for clearance. CL_i is the clearance value in an individual i, CLpop is the clearance value in the population, $f(cov_i)$ is the covariate model which is a function describing the changes in individual clearance values with the individual covariate value (cov_i), ε_i is the unexplained random variability in clearance for an individual i.

$$CL_i = CLpop \times f(cov_i) + \varepsilon_i \quad (1)$$

A covariate model $f(cov_i)$ that describes inter-individual variability in a pharmacokinetic parameter captures the covariation of this parameter and a variable that can be measured in individual patients, so-called covariate [42], thereby reducing the random unexplained variability in a pharmacokinetic parameter.

During covariate model building, the correlation of different variables with individual pharmacokinetic parameters are tested in order to identify statistically significant and clinically relevant covariates [43]. Most common covariates for clearance in paediatrics are bodyweight alone or together with age (post-natal age, post-conceptional or post-menstrual age, and gestational age) [44]. In case these covariates are identified as predictors of clearance ontogeny across the paediatric age range, they can serve as the basis of paediatric dose adjustment (individualized therapy) [45]. In this respect, since the shape of clearance ontogeny can greatly vary with the covariate distribution in the observed data (e.g., age range studied) and with the studied drug and population**,** the evaluation of different covariate relationships is also of importance [43,46,47].

While in this thesis we focus on developmental changes in clearance, other covariates may be of importance in the pharmacotherapy of paediatric patients, similarly as in other populations, such as abnormal body composition, pharmacogenetics, critical illness and inflammatory status, and the impact of these covariates should also be investigated during covariate model building in order to optimize individualized therapy [48].

1.4 Scaling clearance from adults to paediatric patients in absence of paediatric clinical data

While paediatric dose tailoring should ideally be performed based on covariate models built on paediatric clinical data, such information is lacking for first–in-child clinical trials and for drugs administered in paediatric patients but for which no pharmacological study has been undertaken in this population. To cope 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 available adult values, since adult data is normally available before paediatric clinical trials are performed. To date, a diversity of scaling functions has been proposed to scale clearance across the paediatric population (Table 1). These models differ in their covariate, covariate relationship and hypothesis on which they are based.

From all scaling methods available, PBPK is the most accurate method to scale clearance from adults to young children [33], with its accuracy mainly limited in preterm neonates, as the changes in system-specific parameters have not been well characterized in this population. PBPK models quantify how drug properties, characterized by drug-specific parameters, interact with system-specific parameters that reflect anatomical and physiological measures, and account for the impact of diverse ontogenetic changes in system-specific parameters on paediatric pharmacokinetics. However, PBPK scaling is complex and requires accurate measurements of drug-specific parameters. These parameters can be obtained either from *in vitro* experiments, by extrapolating experimental *in vivo* values from animals to humans, by estimation/prediction using specific algorithms [9], or by estimation based on adult clinical data. These measurements are often not available, particularly for existing drugs, and can be biased, which is for instance the case for historical *in vitro* measurements of drug fraction unbound (fu) in plasma [49] and *in vitro* measurements of unbound microsomal intrinsic clearance (CLint) [49,50]. To ensure accurate PBPK scaling from adults to children, these models

require first validation on adult data, in order to overcome problems arising from biased or missing measurements, during which parameters are refined (estimated) such as unbound intrinsic clearance which is otherwise under predicted based on *in vitro* data [10,51]. However, all parameters cannot be estimated due to structural identifiability problems [52], and accurate *in vitro* measurements of some of the parameters might have to be carried out.

Table 1 *Approaches to scale clearance across the paediatric population*

Method	Covariate model	Covariate
AS0.75 [53]	$\left(\frac{BW}{BW\_adult}\right)^{0.75}$	BW
Clark's rule or linear scaling [54,55]	$\left(\frac{BW}{BW\_adult}\right)^{1}$	BW
ADE [56]	$\left(\frac{BW}{BW\_adult}\right)^{k}$ With k equalling 1.1, 1.0, 0.9 and 0.75, for 0 (term neonates)–3 months, >3 months–2 years, >2–5 years and >5 years respectively	BW and PNA
AS0.75+MF_{PBPK} [57]	$\left(\frac{BW}{BW\_adult}\right)^{0.75} \times MF_{PBPK}(AGE)$	BW and AGE
Between drug extrapolation of covariate models [58,59]	Any type of covariate relationship for a drug eliminated by a specific pathway	Any covariate
PBPK [33]	Complex covariate model scaling each physiological parameter, and linking physiological parameters to drug parameters for clearance predictions	PNA and diverse drug properties

AS0.75, allometric scaling using a fix exponent of 0.75; ADE, age-dependent allometric exponent; MF_{PBPK}, isoenzyme maturation function as implemented in PBPK models; PBPK, physiologically-based pharmacokinetics; BW, bodyweight; PNA, post-natal age.

While PBPK is the best scaling method to accurately scale clearance across the paediatric age range, 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. The simplest of these scaling functions solely rely on bodyweight, such as allometric scaling using a fixed exponent of 0.75 (AS0.75) and linear scaling (Table 1). Allometric scaling methods for clearance correlate clearance with size (e.g., bodyweight). Different allometric scaling methods only differ in their allometric exponent which drives the shape of the correlation between clearance and the size descriptor such as bodyweight or body surface area. Because these functions have a poor predictive value in young children, other functions have been proposed.

Inaccuracy of allometric scaling methods often being attributed to the maturational process occurring simultaneously with growth at young ages [47,60,61], Mahmood *et al.* [56,62] have proposed the use of an age-dependent allometric exponent (ADE) in order to account for maturational processes. This method, like AS0.75 or linear scaling, disregards the route of elimination of drugs and can be used to scale clearance of any drug, but relies on the use of different allometric exponents for different age groups. More specifically, with this method, an allometric exponent of 1.1, 1.0, 0.9 and 0.75 is applied for ages 0 (term neonates)–3 months, >3 months–2 years, >2–5 years and >5 years respectively as most recently proposed [56]. More flexible functions than ADE have been proposed to account for the difference in clearance ontogeny of drugs eliminated through different pathways, such as AS0.75+MF_{PBPK} and extrapolation of covariate models between drugs sharing the same elimination pathway (Table 1). AS0.75+MF_{PBPK} has been proposed to scale clearance of drugs undergoing hepatic metabolism. This method 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. Extrapolation of covariate models between drugs sharing the same elimination pathway have been proposed for drugs mainly eliminated by one isoenzyme, but also for drugs undergoing glomerular filtration [63]. For instance, a covariate model describing clearance ontogeny of a drug eliminated through glomerular filtration has been used to predict clearance ontogeny of other drugs eliminated via the same pathway [64]. These functions are semi-physiological covariate models reflecting important mechanisms underlying drug clearance ontogeny [58,59]. Because population PK covariate models are the basis of dose recommendations, this approach would suggest that paediatric dosing recommendations from a drug of which the changes in clearance have been quantified can be

extrapolated to other drugs for which no paediatric PK studies have been undertaken, provided these drugs share the same elimination pathway [65].

1.5 Accurate clearance scaling from adults to paediatric patients: lost in translation

Accurate clearance scaling is important in paediatrics since paediatric dosing regimen of many drugs is derived based on adult clearance scaling due to a lack of paediatric pharmacological data and children may not be subject to dose escalation studies similar to those carried out in adults [66]. While there is a diversity of simple scaling methods available, a clear overview of the applicability of these methods is lacking, leaving clinical pharmacologists without guidance on how to best extrapolate clearance from adult to paediatric patients. Indeed, the accuracy of these different methods has been assessed only on a few case examples, and their comparison to each other is limited due to the use of different types of data, drugs and criterion to assess their accuracy.

AS0.75, which solely relies on the covariate bodyweight, has been recognized as a useful tool to extrapolate clearance from adult values to adolescents [67], but was found to lead to overpredictions in children younger than 5 years [62], reaching up to more than 200 and 3000% in infants and premature neonates, respectively [68]. The latter is often attributed to the maturational process occurring simultaneously with growth at young ages [47,60,61]. ADE, which accounts for maturational processes in young children through the use of different allometric exponents in different paediatric age groups [56,62], was found to lead to prediction error ≤ 63% in children as young as 1 day term neonates based on case examples (n drugs =6) [62].

AS0.75+MF_{PBPK} [57] and extrapolation of covariate models between drugs sharing the same elimination pathway [58,59,64,69,70] both lead to more flexible scaling functions as compared to ADE since differences in maturation (or ontogeny) between different elimination pathways are accounted for. These two scaling methods were found to be accurate in children older than 3 months, and across the entire paediatric age range respectively [57,58,70]. However, both methods have only been investigated for drugs eliminated by one main pathway, while most drug undergo metabolism via several isoenzymes. Moreover, their investigation was limited to CYP3A substrates, and drug eliminated through glomerular filtration or glucuronidation by UGT2B7 respectively [58,59,64,69,70].

In face of this jumble of accuracy assessments, a clear overview of the systematic accuracy of these scaling methods is needed in order to guide their application, which would

ultimately facilitate and accelerate paediatric dose tailoring. 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. This can be investigated using PBPK simulations of clearance ontogeny across the paediatric age range of diverse drugs [59], since paediatric PBPK models link ontogeny in system-specific parameters and drug properties with clearance ontogeny (Figure 2). Developing a decision tree for a rational choice of appropriate clearance scaling methods would ensure accurate scaling of clearance based on the minimum amount of necessary information, making sure that neither important ontogeny processes impacting clearance nor clinicians get lost in translation.

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. For instance, it is known that premature birth can lead to different clearance ontogeny patterns than birth at term. Information on system-specific parameters in these populations is important and currently attempts in developing such models have been published [71]. However, development of such models currently requires an extensive amount of data which is difficult and sometimes impossible to collect in young children, such as hepatic blood flow measurements or intrinsic clearance values for hepatic metabolic routes, and therefore these models need to go through many learn and confirm circles before one can become confident in their predictive performance. Hence, accurate scaling of clearance for different paediatric subpopulations will require development of innovative approaches that can tackle the lack of data on their system-specific parameters.

1.6 Conclusion

There is an urgent need to accurately scale drug clearance in children. Gaining a mechanistic insight on the most important drivers of clearance ontogeny for diverse drugs would enable for the definition of guidance for the application of clearance scaling functions and the development of new ones in order to accurately extrapolate clearance from adults to children. This would ultimately facilitate and accelerate dose tailoring in paediatrics.

References

1. Joseph, P. D., Craig, J. C. & Caldwell, P. H. Y. Clinical trials in children. *Br. J. Clin. Pharmacol.* **79**, 357–369 (2015).

2. Kern, S. E. Challenges in conducting clinical trials in children: approaches for improving performance. *Expert Rev. Clin. Pharmacol.* **2**, 609–617 (2009).

3. Cuzzolin, L., Atzei, A. & Fanos, V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opin. Drug Saf.* **5**, 703–718 (2006).

4. Gore, R., Chugh, P. K., Tripathi, C. D., Lhamo, Y. & Gautam, S. Pediatric Off-Label and Unlicensed Drug Use and Its Implications. *Curr. Clin. Pharmacol.* **12**, 18–25 (2017).

5. Pandolfini, C. & Bonati, M. A literature review on off-label drug use in children. *Eur. J. Pediatr.* **164**, 552–558 (2005).

6. Magalhães, J. *et al.* Use of off-label and unlicenced drugs in hospitalised paediatric patients: a systematic review. *Eur. J. Clin. Pharmacol.* **71**, 1–13 (2015).

7. Tod, M., Jullien, V. & Pons, G. Facilitation of drug evaluation in children by population methods and modelling. *Clin. Pharmacokinet.* **47**, 231–43 (2008).

8. De Cock, R. F. W. *et al.* The role of population PK-PD modelling in paediatric clinical research. *Eur. J. Clin. Pharmacol.* **67 Suppl 1**, 5–16 (2011).

9. Khalil, F. & Läer, S. Physiologically based pharmacokinetic modeling: methodology, applications, and limitations with a focus on its role in pediatric drug development. *J. Biomed. Biotechnol.* **2011**, 907461 (2011).

10. Maharaj, A. R. & Edginton, A. N. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT pharmacometrics Syst. Pharmacol.* **3**, 1–13 (2014).

11. Hartmanshenn, C., Scherholz, M. & Androulakis, I. P. Physiologically-based pharmacokinetic models: approaches for enabling personalized medicine. *J. Pharmacokinet. Pharmacodyn.* **43**, 481–504 (2016).

12. Barrett, J. S., Della Casa Alberighi, O., Läer, S. & Meibohm, B. Physiologically Based Pharmacokinetic (PBPK) Modeling in Children. *Clin. Pharmacol. Ther.* **92**, 40–49 (2012).

13. Fan, J. & de Lannoy, I. A. M. Pharmacokinetics. *Biochem. Pharmacol.* **87**, 93–120 (2014).

14. Mager, D. E., Wyska, E. & Jusko, W. J. Diversity of mechanism-based pharmacodynamic models. *Drug Metab. Dispos.* **31**, 510–8 (2003).

15. Danhof, M. *et al.* Mechanism-based pharmacokinetic-pharmacodynamic modeling: biophase distribution, receptor theory, and dynamical systems analysis. *Annu. Rev. Pharmacol. Toxicol.* **47**, 357–400 (2007).

16. Danhof, M., de Lange, E. C. M., Della Pasqua, O. E., Ploeger, B. A. & Voskuyl, R. A. Mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) modeling in translational drug research. *Trends Pharmacol. Sci.* **29**, 186–91 (2008).

17. Manolis, E. & Pons, G. Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. *Br. J. Clin. Pharmacol.* **68**, 493–501 (2009).

18. FDA. Pediatric Science and Research Activities. Available at: https://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/ucm106614.htm. (Accessed: 23rd February 2018)

19. Krekels, E. H. J. *et al.* Evidence-based drug treatment for special patient populations through model-based approaches. *Eur. J. Pharm. Sci.* **109**, S22–S26 (2017).

20. Di Pietro, M., Cutrera, R., Teleman, A. & Barbaccia, M. Placebo-controlled trials in pediatrics and the child's best interest. *Ital. J. Pediatr.* **41**, 11 (2015).

21. Calvier, E. A. M. *et al.* Drugs being eliminated via the same pathway will not always require similar pediatric dose adjustments. *CPT Pharmacometrics Syst. Pharmacol.* **7**, 175–185 (2018).

22. Sethi, P. K. *et al.* Ontogeny of plasma proteins, albumin and binding of diazepam, cyclosporine and deltamethrin. *Pediatr. Res.* **79**, 409–415 (2016).

23. Matalová, P., Urbánek, K. & Anzenbacher, P. Specific features of pharmacokinetics in children. *Drug Metab. Rev.* **48**, 70–79 (2016).

24. Kearns, G. L. *et al.* Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children. *N. Engl. J. Med.* **349**, 1157–1167 (2003).

25. Lu, H. & Rosenbaum, S. Developmental pharmacokinetics in pediatric populations. *J. Pediatr. Pharmacol. Ther.* **19**, 262–76 (2014).

26. Johnson, T. N. The development of drug metabolising enzymes and their influence on the susceptibility to adverse drug reactions in children. *Toxicology* **192**, 37–48 (2003).

27. Hines, R. N. The ontogeny of drug metabolism enzymes and implications for adverse drug events. *Pharmacol. Ther.* **118**, 250–67 (2008).

28. Salem, F., Abduljalil, K., Kamiyama, Y. & Rostami-Hodjegan, A. Consideringage variation when coining drugs as high versus low hepatic extraction ratio. *Drug Metab. Dispos.* **44**, 1099–1102 (2016).

29. Johnson, T. N., Tucker, G. T., Tanner, M. S. & Rostami-Hodjegan, A. Changes in liver volume from birth to adulthood: a meta-analysis. *Liver Transpl.* **11**, 1481–93 (2005).

30. Guyton, A. C. Cardiac Output, Venous Return, and Their Regulation. in *Textbook of Medical Physiology* (W.B.Saunders, Philadelphia, 1991).

31. Barter, Z. E. *et al.* Covariation of human microsomal protein per gram of liver with age: absence of influence of operator and sample storage may justify interlaboratory data pooling. *Drug Metab. Dispos.* **36**, 2405–9 (2008).

32. Johnson, T. N., Sabzghabaee, A., Rostami-Hodjegan, A. & Tucker, G. T. Prediction of age related changes in midazolam clearance in children. in *Proceedings of the British Pharmacological Society Clinical Pharmacology Section 7-10 January 2003* (ed. Br J Clin Pharmacol) **55**, 418–449 (2003).

33. Johnson, T. N., Rostami-Hodjegan, A. & Tucker, G. T. Prediction of the Clearance of Eleven Drugs and Associated Variability in Neonates, Infants and Children. *Clin. Pharmacokinet.* **45**, 931–956 (2006).

34. Salem, F., Johnson, T. N., Abduljalil, K., Tucker, G. T. & Rostami-Hodjegan, A. A re-evaluation and validation of ontogeny functions for cytochrome P450 1A2 and 3A4 based on in vivo data. *Clin. Pharmacokinet.* **53**, 625–36 (2014).

35. Elmorsi, Y., Barber, J. & Rostami-Hodjegan, A. Ontogeny of Hepatic Drug Transporters and Relevance to Drugs Used in Pediatrics. *Drug Metab. Dispos.* **44**, 992–8 (2016).

36. Emoto, C. *et al.* Characterization of Contributing Factors to Variability in Morphine Clearance Through PBPK Modeling Implemented With OCT1 Transporter. *CPT pharmacometrics Syst. Pharmacol.* **6**, 110–119 (2017).

37. Johnson, T. N. The problems in scaling adult drug doses to children. *Arch. Dis. Child.* **93**, 207–11 (2008).

38. European Medicines Agency. Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. 1–8 (2008). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/ Scientific_guideline/2009/09/WC500003066.pdf. (Accessed: 27th September 2017)

39. European Medicines Agency. ICH Topic E11 Clinical Investigation of Medicinal Products in the Paediatric Population. *CPMP/ICH/2711/99* (2001). Available at: http://www.emea.europa.eu/pdfs/human/ ich/271199en.pdf. (Accessed: 9th March 2018)

40. FDA. Population Pharmacokinetics. *Guidance for Industry* (1999). Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072137.pdf. (Accessed: 9th March 2018)

41. FDA. General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. *Guidance for Industry* (2014). Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425885.pdf. (Accessed: 9th March 2018)

42. Mould, D. R. & Upton, R. N. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. *CPT Pharmacometrics Syst. Pharmacol.* **2**, e38 (2013).

43. Krekels, E. H. J., van Hasselt, J. G. C., Tibboel, D., Danhof, M. & Knibbe, C. a J. Systematic evaluation of the descriptive and predictive performance of paediatric morphine population models. *Pharm. Res.* **28**, 797–811 (2011).

44. Marsot, A., Boulamery, A., Bruguerolle, B. & Simon, N. Population pharmacokinetic analysis during the first 2 years of life: an overview. *Clin. Pharmacokinet.* **51**, 787–98

(2012).

45. Knibbe, C. a J. & Danhof, M. Individualized dosing regimens in children based on population PKPD modelling: are we ready for it? *Int. J. Pharm.* **415**, 9–14 (2011).

46. Piana, C., Danhof, M. & Della Pasqua, O. Influence of covariate distribution on the predictive performance of pharmacokinetic models in paediatric research. *Br. J. Clin. Pharmacol.* **78**, 145–57 (2014).

47. Wang, C. *et al.* The allometric exponent for scaling clearance varies with age: a study on seven propofol datasets ranging from preterm neonates to adults. *Br. J. Clin. Pharmacol.* **77**, 149–59 (2014).

48. Allegaert, K. *et al.* Non-maturational covariates for dynamic systems pharmacology models in neonates, infants, and children: Filling the gaps beyond developmental pharmacology. *Eur. J. Pharm. Sci.* **109**, S27–S31 (2017).

49. Wan, H. *et al.* Impact of input parameters on the prediction of hepatic plasma clearance using the well-stirred model. *Curr. Drug Metab.* **11**, 583–94 (2010).

50. Ye, M., Nagar, S. & Korzekwa, K. A physiologically based pharmacokinetic model to predict the pharmacokinetics of highly protein-bound drugs and the impact of errors in plasma protein binding. *Biopharm. Drug Dispos.* **37**, 123–41 (2016).

51. Maharaj, A. R., Barrett, J. S. & Edginton, A. N. A workflow example of PBPK modeling to support pediatric research and development: case study with lorazepam. *AAPS J.* **15**, 455–64 (2013).

52. Tsamandouras, N., Rostami-Hodjegan, A. & Aarons, L. Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data. *Br. J. Clin. Pharmacol.* **79**, 48–55 (2015).

53. Anderson, B. J., McKee, A. D. & Holford, N. H. Size, myths and the clinical pharmacokinetics of analgesia in paediatric patients. *Clin. Pharmacokinet.* **33**, 313–27 (1997).

54. Clark, A. J. *Handbuch der experimentellen pharmakologie*. (Julius Springer, 1937).

55. Anderson, B. J. & Meakin, G. H. Scaling for size: some implications for paediatric anaesthesia dosing. *Paediatr. Anaesth.* **12**, 205–19 (2002).

56. Mahmood, I. Application of allometric principles in pediatric drug development. in *Fundamentals of Pediatric Drug Dosing* (eds. Mahmood, I. & Burckart, G.) 65–81 (Springer International Publishing, 2016). doi:10.1007/978-3-319-43754-5

57. Strougo, A., Yassen, A., Monnereau, C., Danhof, M. & Freijer, J. Predicting the 'First dose in children' of CYP3A-metabolized drugs: Evaluation of scaling approaches and insights into the CYP3A7-CYP3A4 switch at young ages. *J. Clin. Pharmacol.* **54**, 1006–15 (2014).

58. Krekels, E. H. J. *et al.* From pediatric covariate model to semiphysiological function for maturation: part I-extrapolation of a covariate model from morphine to Zidovudine. *CPT*

pharmacometrics Syst. Pharmacol. **1**, e9 (2012).

59. Krekels, E. H. J. *et al.* From Pediatric Covariate Model to Semiphysiological Function for Maturation: Part II-Sensitivity to Physiological and Physicochemical Properties. *CPT pharmacometrics Syst. Pharmacol.* **1**, e10 (2012).

60. Björkman, S. Prediction of cytochrome p450-mediated hepatic drug clearance in neonates, infants and children : how accurate are available scaling methods? *Clin. Pharmacokinet.* **45**, 1–11 (2006).

61. Edginton, A. N. & Willmann, S. Physiology-based versus allometric scaling of clearance in children; an eliminating process based comparison. *Paediatr. Perinat. Drug Ther.* **7**, 146–153 (2006).

62. Mahmood, I., Staschen, C.-M. & Goteti, K. Prediction of drug clearance in children: an evaluation of the predictive performance of several models. *AAPS J.* **16**, 1334–43 (2014).

63. Knibbe, C. A. J., Krekels, E. H. J. & Danhof, M. Advances in paediatric pharmacokinetics. *Expert Opin. Drug Metab. Toxicol.* **7**, 1–8 (2011).

64. De Cock, R. F. W. *et al.* A neonatal amikacin covariate model can be used to predict ontogeny of other drugs eliminated through glomerular filtration in neonates. *Pharm. Res.* **31**, 754–767 (2014).

65. Krekels, E. H. J., Tibboel, D. & Knibbe, C. A. J. Pediatric pharmacology: current efforts and future goals to improve clinical practice. *Expert Opin. Drug Metab. Toxicol.* **11**, 1679–82 (2015).

66. Johnson, T. N. Modelling approaches to dose estimation in children. *Br. J. Clin. Pharmacol.* **59**, 663–9 (2005).

67. Momper, J. D. *et al.* Adolescent dosing and labeling since the Food and Drug Administration Amendments Act of 2007. *JAMA Pediatr.* **167**, 926–32 (2013).

68. Mahmood, I. Prediction of drug clearance in children from adults: a comparison of several allometric methods. *Br. J. Clin. Pharmacol.* **61**, 545–57 (2006).

69. Zhao, W., Biran, V. & Jacqz-Aigrain, E. Amikacin maturation model as a marker of renal maturation to predict glomerular filtration rate and vancomycin clearance in neonates. *Clin. Pharmacokinet.* **52**, 1127–34 (2013).

70. De Cock, R. F. W. *et al.* Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: towards a semi-physiological function for maturation in glomerular filtration. *Pharm. Res.* **31**, 2643–54 (2014).

71. Claassen, K. *et al.* Development of a Physiologically-Based Pharmacokinetic Model for Preterm Neonates: Evaluation with In Vivo Data. *Curr. Pharm. Des.* **21**, 5688–98 (2015).