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Chapter

1

**General introduction to a novel approach
to characterize developmental changes
in pharmacokinetics across the human
lifespan: application to the prediction of
clearance in children**

1.1. Introduction

Medicine is both an art and a science. In the beginning of Cecil's Textbook of Medicine, it says, "Medicine is a profession that incorporates science and the scientific method with the art of being a physician. The art of tending to the sick is as old as humanity itself. Compared with its long and generally distinguished history of caring and comforting, the scientific basis of medicine is remarkably recent." [1]. Individualized medicine or personalized medicine comprises up-to-date scientific methods that aim to match the right drug to the right patient according to individual characteristics. Dose selection is one of the important issues in individualized treatment, as it determines the efficacy and the safety in the patients who receive the drug.

In paediatrics, selection of the optimal dose is even more crucial, since children are more vulnerable and less tolerant than adults to the drug treatment. However, the knowledge on the variation in the two major determinants of the drug effect, pharmacokinetics (PK) and pharmacodynamics (PD), is limited in paediatrics. Such reality makes that in paediatric clinical practice the dose selection is still empirical and based on mg/kg, despite profound differences in response between children and adults, and between children of different ages, that may or may not be scaling with bodyweight in a linear manner [2].

Pharmacokinetics (PK), which includes the processes of drug absorption, distribution, and elimination, may be referred to as the action of the body on drugs. Pharmacokinetic processes determine the time course of the drug concentration in the circulation, in tissues, and eventually at the target site. Obviously, the knowledge of the variation in pharmacokinetics in children is essential in determining the optimal dose to reach a certain target concentration or exposure.

In addition, the drug concentration-effect relationship, characterizing the pharmacodynamics (PD), determines the intensity of the pharmacological response resulting from the drug treatment. In paediatrics, the concentration-effect or the exposure-response relationship may differ from that in adults. Therefore knowledge of the pharmacodynamics in children is equally important in selecting the optimal dose.

It is not surprising that the PK-PD characteristics of a drug in paediatrics are not the same as in adults, due to physiological differences between adults and children. For example, the gastric pH is neutral (6 to 8) at birth and is acidic (2 to 3) in adults [3]; the total body water content is 80-90% of the bodyweight at birth and is 55-60% in adults [3]; the activity of CYP3A4 is extremely weak or absent in the fetus and begins to rise after birth to reach 30-40% of the adult activity after one month [3]. The differences in PK-PD between adults and children are not straightforward but rather unpredictable because of the complexity of the underlying physiological changes during growth and development. In order to describe how PK-PD characteristics change during the ontogeny process and ideally across the human age-span from birth to adults, mathematical and statistical modeling is needed.

Mathematical modeling must have been used in pharmacology for a long time, although it is hard to tell when the exact start was. The nature of the human learning process, from the observational learning towards the abstract reasoning, makes the application of mathematical modeling in pharmacology inevitable. After a thorough understanding of the mechanism of the underlying process, mathematical models constitute a scientific basis for quantifying and parameterizing the real biological, physiological and pathological processes, which enables the prediction and comparison of the drug effect and individualization of the drug treatment.

Legislation in the United States [4, 5] and in Europe [6] requires that clinical investigations be conducted in paediatric populations. Due to the ethical and practical limitations in paediatric clinical trials, the conduction of the clinical investigation is facing the challenge of evaluating drug efficacy and safety in the paediatric population on the basis of very limited information. Modeling and simulation was soon recognized by drug developers and regulators as the most optimal way to efficiently analyze data and to design clinical trials [4, 6-9]. A paradigm with scenarios for the use of modeling and simulation in paediatric medicines development was proposed, where modeling and simulation was identified as a tool to navigate in the paediatric decision tree and as a study optimization and data analysis tool [8].

Generally, there are two modeling approaches to investigate the changes of the pharmacokinetic characteristics of a drug in human. The first modeling approach is based on observed drug concentrations in blood samples taken in a clinical study and is referred to as the descriptive method or top-down method. The other approach is based on massive physiological and biochemical information, such as enzyme abundance, gastric pH, permeability, blood flow etc. and is referred to as the physiologically based (PB) method or the bottom-up method.

Although discussion and exploration of modeling and simulation (M&S) in paediatric drug development is still ongoing, there is no doubt about the necessity of M&S according to a vote in FDA's Pharmaceutical Science and Clinical Pharmacology Advisory Committee meeting in March 2012, where all voters supported the viewpoint that M&S should be considered in all paediatric drug development programs. As to the modeling and simulation in paediatric drug development, both "top-down" and "bottom-up" modeling approaches are used.

1.2. Top down approach

The top down approach is fitting observations. In pharmacokinetics, observations are the concentrations of the drug. Compartmental pharmacokinetic analysis is the most common top down modeling approach, which simplifies the description of the drug distribution in the human body as a distribution in a number of hypothetical compartments, each with different values of the equilibrium rate constants. This compartmental modeling approach has distinct advantages in predicting or simulating the time course of drug concentrations, since it describes the concentration versus time profile with parameterized differential equations.

Based on the assumption of compartments, two data analysis approaches can be applied: the standard two-stage (STS) approach and the population approach. With the STS approach, PK parameters are, in the first stage, estimated in each individual based on individual concentration time profiles. In the second stage, these parameters are summarized by calculating the mean or median of the parameters and the variability between subjects. A major

drawback of this methodology is that it requires a relatively large number of samples in each individual, while each individual has to contribute roughly the same number of samples. With the STS approach, it is very difficult to distinguish between inter-individual (variability between subjects) and intra-individual or residual variability (variability within one subject, measurement error and model misspecification) and as a result inter-individual variability is often overestimated [10].

In the second approach, the population approach, statistical random variables are added on its structural pharmacokinetic parameters, to account for the inter-individual variability within a population. With the help of these population pharmacokinetic (POPPK) models, we can attribute the variability between individuals in the observed drug concentrations to the variability between individuals in the values of different pharmacokinetic parameters, such as clearance, volume of distribution, absorption rate constant etc. Finally, the inter-individual variability of the pharmacokinetic parameters may be explained by some variables that are related to physiological volumes and functions, e.g. weight or age, in a so-called covariate analysis. In this population approach, the human body system is regarded as a whole in the beginning and is gradually unfolded searching for the physiological cause of the variation in the observed drug concentrations. The uppermost feature of this approach is that it describes or fits the facts, which are drug concentrations.

In paediatrics, clinical studies are more difficult to conduct than they are in adults. Due to ethical and practical issues [11], typically fewer PK samples per individual can be collected during paediatric trials, which results in sparse data for modeling. The population approach is usually preferred for analyzing paediatric PK data because of its capability in dealing with sparse data and in identifying inter-individual variability in paediatric population. Moreover, the population pharmacokinetic approach has been proposed in aiding dose selection in early paediatric development [12]. Besides, Clinical Trial Simulation (CTS) based on available population pharmacokinetic models has been used in the development of an adaptive paediatric clinical trial design [13]. Furthermore, sampling schemes were optimized according to the non-linear mixed effects model based simulation [14] and maximization of the Fisher Information Matrix (FIM) [15] tilde.

One of the most important applications of the top down modeling approach in paediatrics is scaling drug pharmacokinetic parameters (e.g. clearance and volume of distribution etc.) from adults to children. In general, there are three methods for scaling drug pharmacokinetic parameters: allometric scaling, $\frac{3}{4}$ allometric scaling with maturation function, and systematic covariate analysis.

1.2.1. Allometric scaling

Scaling is a term borrowed from engineering, which refers to adaptation of a functional system to operate at different production scales [16]. Similar adaptations of biological function between species and within the human lifespan are needed in pharmacokinetics. Allometry is the study of size and its consequences. The scaling of biological functional systems can be studied and mathematically described on the basis of allometric equations.

$$P = a \times BW^b \quad (1)$$

In the allometric equation, P is the physiological parameter of interest, BW is the bodyweight. The parameters a and b are the allometric constant and the allometric exponent, respectively. This simple equation has been found to be a robust and powerful basis of scientific theory when applied to the analysis of the ecological implications of body size [17]. This theory was thought to be realistic as allometric equations are built empirically using actual observations [18]. Even though there are some biological explanations on this allometric phenomenon [19-21], it is important to realize that the constant b , which is referred to as the allometric exponent, has no physiological meaning by itself [16]. This allometric function has been studied widely in inter-species metabolic rate scaling [22-25] and has been brought into the area of pharmacokinetic modeling for the scaling drug clearance and volume of distribution [26]. In the population pharmacokinetic modeling, the allometric equation is adapted as follows [18]

$$P_i = P_{std} \times \left(\frac{BW_i}{BW_{std}} \right)^b \quad (2)$$

in which P_i is the individual PK parameter in a subject with a bodyweight of BW_i and P_{std} is the PK parameter of a standardized individual with a bodyweight of BW_{std} . The adapted allometric equation (equation 2) is the most frequently

used covariate model structure in population pharmacokinetic modeling for describing changes in PK parameters between adults and children.

For paediatric studies, it has been proposed that the allometric exponent b should be fixed to the value of 0.75 for the scaling of drug clearance and to the value of 1 for volume of distribution to account for differences in size, no matter whether it is applied to adults or children [18]. This view is based on the allegedly substantial experimental evidence for these values of the allometric exponent in biology. Indeed many studies have reported values of the estimated allometric exponent for clearance that are close to 0.75. However, the allometric equation with the fixed value of 0.75 for clearance, referred to as $\frac{3}{4}$ allometric equation, has been challenged by different researchers [27, 28]. The challenges are mostly on the basis of the argument that the value of 0.75 should be the universal allometric exponent for clearance, while many studies have shown that use of the $\frac{3}{4}$ allometric equation yields discrepancies between observed versus predicted concentrations in very young children [29-31].

In this respect, Mahmood systematically investigated the predictive performance of scaling methods with different allometric exponent values (0.75, 0.8, 0.85 and 1) across the whole paediatric age-span for 41 drugs [27]. Clearances reported from literature were compared with allometric model predicted clearances with different exponent values. He found that all methods exhibited uncertainty in the prediction of the drug clearance in children and that no single method was suitable for all drugs for all age groups. The study also indicates that a single exponent may not be suitable for the prediction of drug clearance in children of all ages from adult data; therefore, a combination of methods is recommended in order to improve the prediction. It appears that for children ≤ 1 year old, a better approach is to use no exponent (exponent = 1) on the ratio of children and adult body weight. Specifically, allometric exponent values close to or above 1 were estimated for scaling clearances in young children [27]. After age 5, one can use any of the three exponents (0.75, 0.80 and 0.85) to achieve a reasonably good prediction of clearance in children [27].

1.2.2. $\frac{3}{4}$ Allometric scaling with maturation functions

In paediatric POPPK modeling, age may also have an influence on the inter-individual variability of drug clearance, especially in young children, infants and

neonates. This influence can be explained as the reflection of changes during the ontogeny in the physiological mechanism related with maturation instead of size. However the distinction between age and bodyweight as the basis for the scaling is complicated by the fact that age and bodyweight are correlated in a highly nonlinear manner. Consequently, in the covariate analysis of POPPK modeling, the apparent influence of age on the value of clearance may be contaminated by the influence from bodyweight and vice versa. Therefore, it has been proposed to separate the influence of bodyweight and age effect by using the $\frac{3}{4}$ allometric equation in the covariate analysis for clearance to account for size [26]. To account for the influence of maturation, an asymptotic exponential maturation function for clearance, incorporating postnatal age, has been proposed, which is incorporated as a multiplicative factor in the $\frac{3}{4}$ allometric equation based on body weight [32].

$$CL_i = CL_{std} \times \left(\frac{BW_i}{70}\right)^{0.75} \times \left(1 + \beta \times e^{\left(-AGE_i \times \frac{\ln 2}{t}\right)}\right) \quad (3)$$

$$MF = 1 + \beta \times e^{\left(-AGE_i \times \frac{\ln 2}{t}\right)} \quad (4)$$

In this equation β is the parameter reflecting fractional difference from the CL_{std} at birth. The parameter t is the parameter describing half-times of age-related changes in clearance. It is worthy to note that parameter β should be constrained between -1 and 0 so that the maturation factor (MF) will start from $1 + \beta$, which is less than 1, at birth and gradually approach to 1 with adult age.

A modified version of equation 3 was used to describe acetaminophen (paracetamol) age-related clearance maturation, in the basis of postconception age (PCA) [33].

$$CL_i = CL_{std} \times \left(\frac{BW_i}{70}\right)^{0.75} \times \left(1 + \beta \times e^{\left(-(PCA_i - 28) \times \frac{\ln 2}{t}\right)}\right) \quad (5)$$

In this equation, β is the parameter reflecting fractional difference from the CL_{std} at postconception age of 28 weeks. Postconception age rather than postnatal age was regarded to be a better predictor because the maturation of clearance begins before birth. Postmenstrual age (PCA) can also be used in the maturation function and the differences in PMA and PCA are expected to be 2 weeks in average [34].

As the asymptotic exponential maturation function has poor properties for extrapolation, later on a hyperbolic function has been proposed as the maturation function in the $\frac{3}{4}$ allometric scaling model [35].

$$MF_{PMA} = \frac{PMA^{Hill}}{PMA^{Hill} + MATCL_{50}^{Hill}} \quad (6)$$

Maturation functions on the basis of age as covariate seem to help to account for the discrepancy from the $\frac{3}{4}$ allometric equation in young children and can be used to describe the changes in clearance across a large age-span. However, it was also reported to have a poor predictive power of clearance in preterm and term neonates, infants and very young children [36, 37]. In addition, incorporating the combination of two correlated covariates in the nonlinear mixed effect model may result in bias in parameter estimates [38]. Recently, it has been shown that when one of two correlated covariates that contain information about a model parameter is pre-selected over the other, the predictive performance of the resulting model may be diminished, unless the pre-selected covariate relationship reflects the true biological relationship [39]. Although there are examples of the successful use of the $\frac{3}{4}$ allometric equation in the adult population, it has been shown to be unreliable in young children [27-31]. The colinearity between the bodyweight and age covariates and its consequences, therefore, become a concern when it is used as a descriptive reference model for clearance.

1.2.3. Systematic covariate analysis

In population pharmacokinetic modeling, a covariate analysis does not only comprise the identification of covariates that significantly influence the PK parameters but also includes the shape of the relationships between covariates and parameters. In the $\frac{3}{4}$ allometric scaling approach with maturation functions, the shape of the relationship between bodyweight and clearance is not determined by the data but is fixed *a priori*. In contrast to this approach, a data-driven systematic covariate analysis approach without any *a priori* assumption was proposed in paediatric modeling [40]. In the systematic covariate analysis, covariates are plotted independently against the empirical Bayesian estimates (EBE) of PK parameters, which provides graphical aids in identifying the most appropriate covariate equation. Covariate equations can be tested from the simplest linear function to complicated nonlinear functions such as Generalized Additive Model (GAM). Potential covariates are separately

tested and are considered statistically significant if the objective function decreased 7.9 points [40]. When more than one significant covariate for the simple model is found, the covariate-adjusted model with the largest decrease in objective function is chosen as a basis to subsequently explore the influence of additional covariates by means of the same criteria [40]. Covariates can be stepwise included into or excluded from the model depending on the model building strategy and the number of the candidate covariates. However, the final covariate model should be confirmed by the absence of unexplained inter-individual variability from covariates, which can be illustrated by the absence of a trend in the plot of EBE inter-individual (η) against the covariate [41].

An example of such a systematic covariate analysis approach was reported in a study of morphine glucuronidation clearance in preterm neonates, infants and children younger than 3 years [40]. The final model was reported to be the best model for describing the changes in morphine glucuronidation clearance within the study age-span [42]. Later on, this model was externally validated [43] and proved to be applicable across drugs that share same metabolism pathway mediated by UGT2B7 enzymes [44]. Paci *et al.* also applied such systematic covariate analysis in a research for busulfan in 205 children from 10 days to 15 years [45]. After testing different covariate models for clearance, they found that the allometric scaling model with the exponent value of 1.25 for bodyweight less than 9 kg and 0.76 for greater than 9 kg was the best covariate model [45].

1.3. Bottom up approach

In contrast with the top-down approach, the physiologically based approach looks at the pharmacokinetics from the underlying mechanism. The general concept of PBPK modeling is to mathematically describe relevant physiological, physicochemical, and biochemical processes that determine the pharmacokinetic behavior of a compound in as much detail as is appropriate or needed [46]. In paediatrics, unlike top-down approaches that require the availability of age-appropriate observed data, bottom-up approaches are used at a stage when these data have yet to be generated. Knowledge-driven or bottom-up approaches are based on the integration of various types of information (e.g. *in vitro* data, physiological and anthropometric information,

and drug physicochemical properties) with a model that structurally mimics the functioning of the biological system including relevant organ system(s) [47]. Chen and Gross [48] and Himmelstein and Lutz [49] discuss the rationale and history behind the development of PBPK models and report examples of the first PBPK models. Khalil and Läer provided a general overview of the structure of PBPK models as well as their applications and weaknesses [46]. Most recently, Barrett *et al.* gave a review of the PBPK modeling specialized on its application in paediatric drug research [50].

Physiologically Based Pharmacokinetic (PBPK) models have been applied for the selection of the first-in-children dose in paediatric drug development. Edginton reviewed the knowledge-driven PBPK approaches for the guidance of first-in-children dosing [47] and proposed a workflow of the application of PBPK in paediatric drug development together with Maharaj and Barrett [51]. Additionally, Johnson and Rostami-Hodjegan pointed out other potential applications of the PBPK model, where the conduct of studies is not feasible (e.g. drug-drug interactions in paediatric populations, particularly those with varying genotypes or renal function compared to average individuals) [52].

Interest in PBPK modeling in the field of paediatric drug development has been increasing recently. However, there are still skepticisms about the predictive performance of the PBPK models in paediatric drug development. The main concerns about the PBPK models are on the reliability of the resources to build PBPK models and the knowledge gap between *in vitro* and *in vivo*, between adults and children. Specifically, the PBPK model prediction in young children is less confident as some physiological information, such as enzyme activity, in those populations is not available. Leong *et al.* reviewed data relating to PBPK modeling and simulation in submissions to FDA made during the years 2009 - 2011 with respect to four paediatric drugs, as well as research on the use of PBPK tools with respect to several model agents used across varying age groups [53]. They found that PBPK models could not accurately predict weight normalized clearance values (CL_{BWnorm}) for all paediatric groups [53]. They urged that there is a critical need to refine paediatric PBPK models [53]. The request of the refinement of PBPK models not only comes from regulators but also arose from clinicians, who reminded us not to get PBPK modeling too disconnected from the "*in vivo*" world of paediatric developmental pharmacology [54].

1.4. Descriptive and predictive performance of paediatric models

For all pharmacokinetics models, either descriptive or mechanistic, the performance in describing observations should be demonstrated. In nonlinear mixed effect models, a large number of methods have been proposed for diagnosing, evaluating and validating various aspects of the model performance. Where possible all these methods should be considered in building a descriptive model. Generally, the more validations a model goes through, the more reliable the model is. External validation, incorporating data that have not been used to build the model, is preferred over internal validation. However, we should be aware that a model is always developed based on data collected in distinct study settings, which are determined by factors such as the inclusion criteria of patients, the design of the study and the distribution of covariates. For the external data these settings may be different, leading to models that differ from the original. One can never make sure that a model is valid in the next new dataset even if the model has been validated internally and externally before. Model validation results are always reliable within certain constraints. Having noticed the limitation of the model validation, we should always be aware of the importance of the necessary model validations as they are helping us to determine whether the model is appropriate for the data it is built on.

In paediatrics, evaluation of pharmacokinetic models are especially important due to the heterogeneity in paediatric populations and the fact that paediatric datasets are typically sparse [11]. However, paediatric models were seldom evaluated adequately in the past [55]. Amongst all model validation methods, some aspects are especially important. This concerns in particular the model for scaling of the PK parameters over a large age-span. Krekels *et al.* have proposed a scheme of systematic model evaluation approaches for paediatric pharmacokinetic modeling, which covers all the important aspects [42].

The fit of the model to the drug concentration is always the first aspect to be evaluated in pharmacokinetic modeling, since good concentration prediction is the basic requirement for a PK model. Usually, the goodness-of-fit is evaluated through the visual inspection of graphs [56] including i) observed (OBS) versus

individual predicted (IPRED) concentrations, ii) OBS versus population predicted (PRED) concentrations, iii) conditional weighted residual error (CWRES) versus time, and iv) CWRES versus PRED. The OBS versus PRED plot is specifically important as it reflects whether the whole population model (comprising structure model and covariate model) is adequate. In a model covering a large age-span, the OBS versus PRED plot needs to be stratified between age groups for further examination of whether the adequacy is the same for individuals in different age ranges. However, the stratified OBS versus PRED plot cannot help in identifying the cause of the bias in itself, as it reflects sum effects of all pharmacokinetic parameters. In population pharmacokinetic modeling with the First Order approximation Conditional Estimation (FOCE) algorithm, empirical Bayesian estimates (EBE) provide post hoc individual parameters of pharmacokinetic parameters (clearance or volume of distribution). This EBE is not only useful for predicting individual concentrations but is also helpful in covariate model building and diagnosis. Specifically, plots of *post hoc* inter-individual variability of a PK parameter versus covariates may be used to check whether there is a covariate relationship. Moreover, plots of *post hoc* estimates of a PK parameter versus covariates facilitate the identification the shape of the covariate relation. Eventually, an adequate covariate model should be confirmed by the absence of correlation between covariates and inter-individual variability of the concerned PK parameters [41]. However, the evaluation based on the EBE should be done with caution if there is a high shrinkage of the EBE inter-individual random effect, defined as η -shrinkage [57]. High η -shrinkage usually occurs when few data are available from an individual [41] and may mislead the covariate relationships finding [58]. This is particularly important in paediatric investigations, as they may typically contain sparse data.

Simulation based model validations or evaluations play an important role in POPPK modeling. A visual predictive check (VPC) is a commonly used for model validation in adults [59], which illustrates lines for the median values and their 90% prediction interval based on 100 to 1,000 times simulation of concentration-time profiles. The observed values in the internal or external dataset are subsequently plotted on top of this. It can then be visually checked whether 90% of the observations are within the indicated prediction interval and whether there is no bias in the observations compared with the prediction

interval. The VPC is a simulation-based diagnostic that can be used when the PK or PD profiles for all individuals in the dataset are similar and it allows for easy interpretation of the result. For this diagnostic tool, there are no statistical tests and all evaluations are based on visual assessment.

Although the VPC can also be used for the evaluation of paediatric models, when data are obtained during routine clinical practice and variability in individual dosing and sampling schemes are high, a (normalized prediction distribution error) NPDE methodology [60] is often easier to perform and interpret. This method yields information on how accurate the model predicts the median value of the observations and the variability within them. The interpretation of this diagnostic is less straightforward than for the VPC, but the advantage of this method is that it can be used when the variability in dosing regimen (both in time, amounts and rates) is high or when there is a large number of covariates in the model. This can for instance be the case for data obtained during routine paediatric clinical practice.

Model predictive performance usually refers to the capability of a model in predicting true measurements [61]. In paediatric pharmacokinetic models, true measurements are concentration profiles. Therefore, the goodness-of-fit plot is an evaluation method of the predictive performance of the whole pharmacokinetic model, which comprises the structure model, statistical models and covariate models. Besides, another predictive performance may be evaluated if the empirical Bayesian estimates (EBE) of pharmacokinetic parameters are regarded as the true individual measurements predicted by covariates. Actually, the predictive performance of the covariate models can be visually inspected by the plot of individual *post hoc* parameters against covariates superimposed with covariate model predicted curves. However, two numerical quantities of this predictive performance, mean squared prediction error (MSE) and root mean squared prediction error (RMSE), are more preferable in comparing different covariate models [61].

$$MSE = \frac{1}{n} \sum_{i=1}^n (predicted_i - true_i)^2 \quad (7)$$

$$RMSE = \sqrt{MSE} \quad (8)$$

The definitions of those two quantities are expressed in equation 7 and equation 8. The root mean squared prediction error (RMSE) can be expressed as percent of mean true measurements (%RMSE) using equation 9 as follows [37].

$$\%RMSE = \frac{RMSE \times 100}{\frac{1}{n} \sum_{i=1}^n true_i} \quad (9)$$

1.5. Discussion and conclusion

Drug prescription in the paediatric population is still very empirical while there is an urgent need for evidence based dosing in children. In pharmacokinetics, both population pharmacokinetics (POPPK) models and physiologically based pharmacokinetics (PBPK) models can describe and/or predict drug concentration time profiles and facilitate drug development and clinical practice.

The population pharmacokinetic approach is aiming to fit clinical observations. Paediatric POPPK model is usually based on a relatively large clinical dataset from a large number of different individuals, while the paediatric physiologically based model (PBPK) is based on relatively limited physiological data coming from published or unpublished *in vitro* studies. Although clinical samples are difficult to collect in paediatric populations because of the ethical and practical reasons, POPPK model can still utilize these sparse data efficiently and derive reliable results. Not only can POPPK model estimate the mean values of pharmacokinetic parameters over a population, it can also provide the distribution of those parameters, which is useful for clinical trial simulations. However, due to the absence of physiological mechanisms, POPPK model results are restricted to specific drugs or populations and can not be extrapolated to other drugs. A combination of the POPPK approach and PBPK approach is naturally the best solution. Krekels *et al.* elaborated on combining PBPK and POPPK approaches in order to identify the influence of changes in the system- and drug- specific parameters on the net maturation of *in vivo* UGT2B7-mediated glucuronidation [62]. In the end, they suggested that the maturation profile for UGT2B7 ontogeny in a PBPK model can be improved based on information obtained from a covariate model of a paediatric population model derived for a specific substrate for UGT2B7 on the basis of a systematic covariate analysis [62].

Such a combination of POPPK and PBPK approaches may be important particularly for paediatric drug development, where dose selection may be determined based on PBPK model simulation. The PBPK model for dose selection in the development of a new drug can be refined by the results of covariate functions from POPPK models of probe drugs sharing the same physiological mechanism as the new drug. Moreover, with the help of POPPK model, physiological parameters in PBPK models can be scaled to certain paediatric populations where no *in vitro* information is available. Therefore, developing a POPPK model covering the age-span from birth to adult with good descriptive performance all across is of great value. For this, a novel approach is proposed given the described limitations of the $\frac{3}{4}$ allometric scaling model and its derivative maturation model.

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