



Physiologically-based pharmacokinetic models for children: Starting to reach maturation?



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ABSTRACT

Developmental changes in children can affect the disposition and clinical effects of a drug, indicating that scaling an adult dose simply down per linear weight can potentially lead to overdosing, especially in very young children. Physiologically-based pharmacokinetic (PBPK) models are compartmental, mathematical models that can be used to predict plasma drug concentrations in pediatric populations and acquire insight into the influence of age-dependent physiological differences on drug disposition. Pediatric PBPK models have generated attention in the last decade, because physiological parameters for model building are increasingly available and regulatory guidelines demand pediatric studies during drug development. Due to efforts from academia, PBPK model developers, pharmaceutical companies and regulatory authorities, examples are now available where clinical studies in children have been replaced or informed by PBPK models. However, the number of pediatric PBPK models and their predictive performance still lags behind that of adult models. In this review we discuss the general pediatric PBPK model principles, indicate the challenges that can arise when developing models, and highlight new applications, to give an overview of the current status and future perspective of pediatric PBPK modeling.

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Contents

1. Introduction.	1
2. Pediatric PBPK model development	3
3. Use of models to mechanistically describe ADME processes	3
4. 4 Exploratory pediatric PBPK models.	8
5. Physiologically-based toxicokinetic models.	9
6. Quality control	9
7. Regulatory applications.	10
8. Future perspectives	10
9. Conclusion	11
References	11

1. Introduction

New drugs require pediatric studies as part of their market authorization, while marketed drugs often lack information on pediatric efficacy, safety and dosing (EMA, 2007; FDA, 2002/2003; Frattarelli, et al., 2014; Sachs, Avant, Lee, Rodriguez, & Murphy, 2012). To find out what doses are suitable for different age groups, it is important to realize that many developmental processes are not reflected by simple scalars

Abbreviations: CYP, cytochrome P450; DDI, drug-drug interaction; GFR, glomerular filtration rate; GST, glutathione s-transferase; kp, tissue-plasma partitioning coefficient; mAB, monoclonal antibody; OAT, organic anion transporter; OCT, organic cation transporter; PBPK, Physiologically-based pharmacokinetic; UGT, UDP-glucuronosyltransferase.

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like body weight or body surface area (Cella, Knibbe, Danhof, & Della Pasqua, 2010). Drug metabolizing enzyme or transporter activity show protein-specific and organ-dependent developmental profiles (Daood, Tsai, Ahdab-Barmada, & Watchko, 2008; Lam et al., 2015; Mooij et al., 2014; Sadler et al., 2016; Upreti & Wahlstrom, 2016; van Groen et al., 2018). Moreover, other processes involved in the disposition of drugs also change in a nonlinear relationship with growth and development, as was reviewed recently (van den Anker, Reed, Allegaert, & Kearns, 2018).

Modeling and simulation has evolved as one of the cornerstones of pediatric drug development by making optimal use of available data (Manolis et al., 2011). In population PK (popPK) models, parameters are computationally scaled/fitted in order to best describe *in vivo* measured drug concentrations. In this approach patient-specific characteristics can be identified allowing for a more individualized therapy, although a robust estimation of population PK parameters requires relatively rich pharmacokinetic data, especially when multiple characteristics/co-variables are studied. Moreover, a PopPK parameter will reflect a combination of several physiological and drug-related processes, which is difficult to extrapolate to other populations or drugs (Brussee et al., 2018; Brussee et al., 2018). PBPK models provide mechanistic PK predictions and although the derivation of the required parameters could be challenging, theoretically they are more suitable for between-population or between-drug PK predictions (W. Zhou et al., 2018; W. Zhou et al., 2016). Integrating developmental changes in PBPK models has proven to be successful in predicting doses across the pediatric age span (Leong et al., 2012; Mansoor, Ahmad, Alam Khan, Sharib, & Mahmood, 2019). More specifically, regulatory authorities have also acknowledged the added value of these models and

encourage their use in pediatric drug development (Leong et al., 2012). The development of PBPK and/or PopPK models is in accordance with FDA regulations (e.g. pediatric decision tree) as in any case pediatric drug pharmacokinetic (PK) and safety data need to be evaluated in order to bridge from the adult to the pediatric population.

1.1. PBPK modeling in adults and children

PBPK models represent the body as anatomically and physiologically recognizable compartments in which the processes of drug absorption, distribution, metabolism and excretion (ADME) are described with a set of differential equations. PBPK models provide a mechanistic framework that separately includes physiological parameters (often also referred to as system specific parameters), drug-related parameters, and parameters reflecting trial design, which aims to cover the complex processes governing drug disposition (Fig. 1). Models range from a simple minimal setup, consisting of only a few essential compartments, to full-body PBPK models in which all major organs in the body are represented by compartments connected through blood flow (Kuepfer et al., 2016; Upton, Foster, & Abuhelwa, 2016). Much progress has been made in accurately expressing the relevant physiological processes in terms of accurate parameters. While PBPK models usually consist of many parameters and developing a model may be labor intensive, previous models can be used to build upon as physiological parameters are not expected to change within a population of interest, which markedly reduces the effort that is needed for model building (Rostami-Hodjegan, 2012). Next to the physiological parameters, a variety of drug-related data affecting pharmacokinetics need to be obtained, which largely can be generated by *in vitro* experiments (Fig. 1).

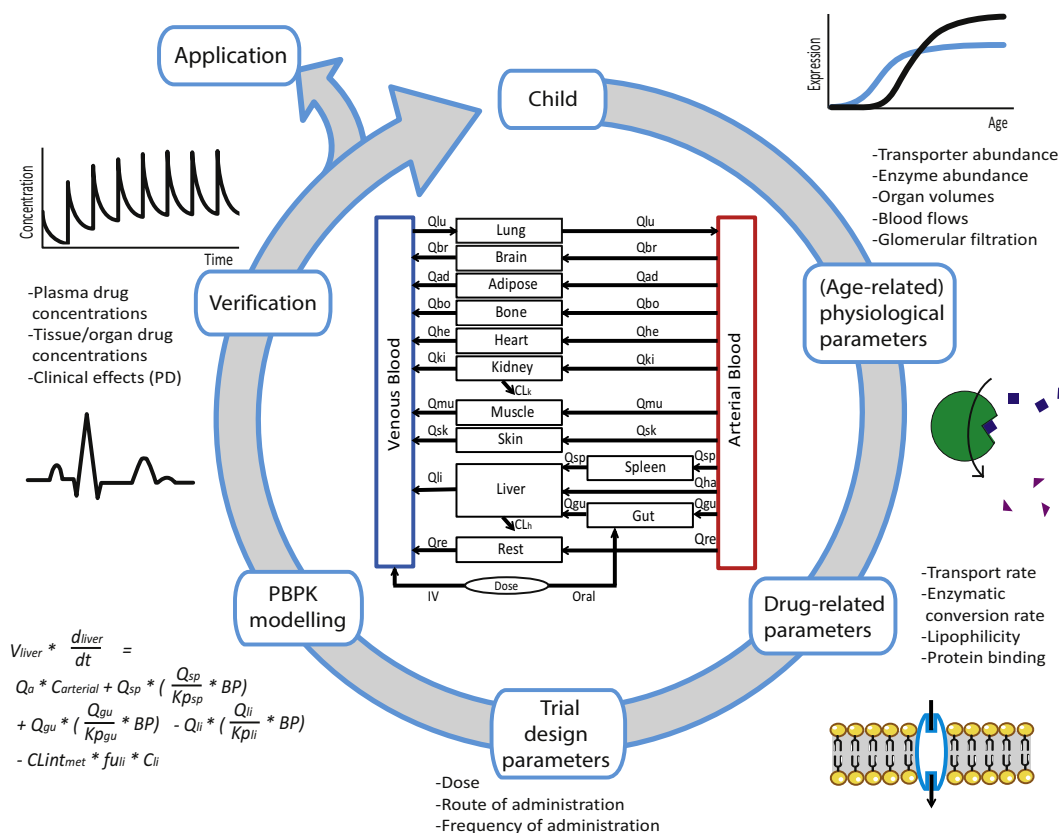


Fig. 1. “Learn, confirm and apply” development cycle used to build and optimize pediatric PBPK models based on physiological, drug-related and trial design parameters. Q_{lu} , Q_{br} , Q_{ad} , Q_{bo} , Q_{he} , Q_{ki} , Q_{mu} , Q_{sk} , Q_{sp} , Q_{gu} , Q_{ha} , Q_{re} , Q_{li} denote blood flows towards, lung, brain, adipose tissue, bone, heart, kidney, muscle, skin, spleen, gut, liver (arterial flow), rest of tissues, and from liver, respectively (e.g. $Q_{lu} = 300 \text{ L} \cdot \text{h}^{-1}$ in adults). Physiological (system) parameters, drug-related parameters and trial-design parameters are separately included in PBPK models.

Models can be adjusted to other populations by changing the population-dependent system parameters. They have successfully been translated from animals to humans (Ball, Bouzom, Scherrmann, Walther, & Decleves, 2012; Bi, Deng, Murry, & An, 2016; Lukacova et al., 2016; Parrott et al., 2011), from Caucasians to different ethnicities (Feng et al., 2016; Matsumoto et al., 2018), and from healthy to diseased populations (Radke et al., 2017; Rasool, Khalil, & Laer, 2015; Rhee, Chung, Yi, Yu, & Chung, 2017). Similarly, extrapolations from adults to children are based on adapting age-dependent adult physiological parameters to values appropriate for children. This approach is commonly applied in the development of pediatric models to evaluate key pharmacokinetic processes and confirm age-unrelated drug-dependent parameters in an adult population, before introducing age-related pediatric physiological parameters, for which data can be more sparse (Maharaj & Edginton, 2014).

Pediatric PBPK modeling has developed from 'proof of principle' to a valuable tool for the prediction of pharmacokinetics in children (Yellepeddi et al., 2018). Even more, PBPK-PD (PBPK-pharmacodynamic) modeling is increasingly used to predict drug effects. The increased interest is also reflected by an exponential rise in the number of publications on this topic during the last decade. On the other hand, the number of pediatric PBPK models and their predictive performance still lags behind adult models (Grimstein et al., 2019; Jamei, 2016; Sager, Yu, Ragueneau-Majlessi, & Isoherranen, 2015; Templeton, Jones, & Musib, 2018). The aim of this review is to (1) discuss the use of pediatric PBPK models for different purposes and identify challenges in model building, (2) provide key considerations to evaluate pediatric PBPK model quality, and (3) to give a future perspective on model development that will further increase their quality and acceptance, as well as their wider applicability into clinical care.

2. Pediatric PBPK model development

A tutorial for a general workflow to develop a pediatric PBPK model was described by Maharaj et al. and will not be further discussed here (Maharaj, Barrett, & Edginton, 2013; Maharaj & Edginton, 2014). Trends between adult and pediatric physiological parameters are summarized in Table 1.

In general, it is considered good practice to develop an adult model first before a pediatric model is built, to obtain insight into key pharmacokinetic processes and allow for the verification of age-independent drug-related parameters. Some of the physiological parameters that are subsequently included in the pediatric model are well established, such as organ volumes, however, information on others can be sparse or absent (e.g. transporter expression). This indicates that dependent on the route of administration (e.g. oral versus intravenous dosing) and the drug involved (e.g. CYP3A4 substrate versus UGT substrate) confidence in the model-predicted outcomes will be determined by the (un)certainly of the estimates for the included parameters. Although important information gaps may exist in ADME-related physiology for specific drug models, a pediatric PBPK model can be judged 'fit for purpose' if the relevant patterns related to age can be described and sufficiently verified with clinical data.

For pediatric model development, it is valuable to obtain PBPK drug-specific parameters from human *in vitro* studies that can be scaled to *in vivo* parameters (*in vitro-in vivo* extrapolations (IVIVE), or also called "bottom up approach"). For example, an *in vitro* clearance value can be calculated from recombinant drug metabolizing enzyme activity, which is subsequently scaled to whole liver clearance by taking into account age-appropriate liver weight and enzyme expression per gram. Such an approach can contribute to the development of first in child dosing regimens in case it is not possible to scale or fit parameters based on comparison of predicted model output with measured drug concentrations. In addition, it results in better mechanistic insight into the underlying ADME processes, for example the relative contribution of individual drug metabolizing enzymes in clearance (Jaroch, Jaroch, &

Bojko, 2018; Johnson et al., 2018; Scotcher, Jones, Posada, Rostami-Hodjegan, & Galetin, 2016).

In practice, a combination of *in vitro* data and *in vivo*-derived drug concentrations are often used for model parametrization. If physiological or drug-related parameters for PBPK models are not available, they need to be scaled or fitted based on clinically measured drug concentration data. This "middle out approach" allows the quantification of processes affecting PK and to explore potential differences between adults and children (Emoto, Johnson, McPhail, Vinks, & Fukuda, 2018; Zane & Thakker, 2014). Similarly, pediatric models will also benefit from adult *in vivo* pharmacokinetic data. For instance, adult clearance values can be used to estimate pediatric clearances if differences in enzyme expression and activity of the elimination pathways involved are taken into consideration.

3. Use of models to mechanistically describe ADME processes

3.1. Absorption

Oral dosing is the preferred route of drug administration in children. Multi-compartment absorption models are used to predict drug absorption from different gut segments, in which the complex interplay between different physiological processes and their effect on absorption is incorporated. Age-related processes accounted for oral absorption in PBPK models are gastric emptying time, small and large intestinal transit time and intestinal surface area, which are only part of the physiological processes subject to developmental differences (Table 2). Recently, a gastro-intestinal model was built by Johnson et al. based on a review of the literature. They recognized knowledge gaps in the ontogeny of fluid volume dynamics in the GI tract, intestinal bile flows, and CYP enzyme and transporter expression. Nevertheless, disposition of the relatively high solubility and permeability drugs, paracetamol and theophylline, were predicted with good precision. In addition, accurate predictions were also made for the low solubility drug ketoconazole and carbamazepine. (Cristofolletti, Charoo, & Dressman, 2016; Johnson, Bonner, Tucker, Turner, & Jamei, 2018; Kohlmann, Stillhart, Kuentz, & Parrott, 2017) (Table 2).

Intestinal protein ontogeny data for CYP3A4 show a developmental increase in activity when children mature, whereas expression of the eflux transporter P-glycoprotein appears to be stable from fetal age until adulthood (Table 1, Fig. 2) (Johnson, Tanner, Taylor, & Tucker, 2001; Konieczna et al., 2011). Knowledge on intestinal abundance of other drug metabolizing enzymes and transporters is still limited. In that case PBPK models are useful in combination with measured clinical drug concentrations to explore developmental differences in enzyme and transporter expressions that have not yet been characterized at the protein level.

Models describing other routes of absorption such as dermal, pulmonary and ocular drug absorption were developed previously for adults, rodents and rabbits, however, for children they are scarce (Le Merdy et al., 2019; Poet et al., 2000; Salar-Behzadi et al., 2017; Valcke & Krishnan, 2010). One study described multi-route (oral, dermal, pulmonary) exposure to drinking water toxicants in neonates and children, providing proof of principle also for other xenobiotics including drugs (Valcke & Krishnan, 2010).

3.2. Distribution

Once in the systemic circulation, a drug will be distributed to organs and tissues, which is usually described in PBPK models by the (predicted) tissue-plasma partitioning coefficient (K_p) (Table 3) (Poulin & Theil, 2000; Rodgers, Leahy, & Rowland, 2005; Rodgers & Rowland, 2006). Age-appropriate calculations of the K_p value of a drug is dependent on the fractional volumes of tissue water and lipid, as well as fraction of the compound which is unbound in plasma. In general, neonates and young children will have a higher percentage of tissue water and

Table 1
Developmental trends in physiological parameters.

ADME process	Physiological parameter	Developmental pattern	Age range reported	Ref.
Absorption	Small intestinal length ^a	Increase	Fetuses-adult	(Gondolesi et al., 2012; Struijs, Diamond, de Silva, & Wales, 2009; Weaver, Austin, & Cole, 1991)
	Large intestinal length ^a	Increase	Neonates-adolescents	(Koppen et al., 2017; Mirjalili, Tarr, & Stringer, 2017)
	Gastric pH	Stable, subject to alkalinization by milk feeds	Neonates-adolescents	(Avery, Randolph, & Weaver, 1966; Schmidt et al., 2015; Whetstine, Hulsey, Annibale, & Pittard, 1995)
	Small intestinal pH	Stable	Neonates-children	(Barbero et al., 1952; Fallingborg et al., 1990)
	Gastric emptying	Stable	Neonates-adults	(Bonner et al., 2015)
	Gut transit time	Stable	Neonates- adults	(Maharaj & Edginton, 2016)
	Intestinal membrane transporters		Fetuses-adults	(Konieczna et al., 2011; Mizuno et al., 2014; Mooij et al., 2014)
	- Pgp ^{b,c}	Stable		
	- BCRP ^c	Stable		
	- MRP1 ^c	Stable		
	- MRP2 ^b	Stable		
	- OATP-2B1 ^b	Decrease		
	Intestinal drug metabolizing enzyme		Fetuses-adults	(Fakhoury et al., 2005; Johnson et al., 2001)
- CYP3A4 ^c	Increase			
Distribution	Tissue composition		Fetuses-children	(Butte, Hopkinson, Wong, Smith, & Ellis, 2000; Carberry, Colditz, & Lingwood, 2010; Malina, 1969)
	- Protein ^d	Stable	2 years of age	
	- Water ^d	Decrease		
	- Fat ^d	Increase		
	Organ volumes ^a	Increase	Neonates-adults	(Ogiu, Nakamura, Ijiri, Hiraiwa, & Ogiu, 1997)
	Organ blood flow		Neonates-adults	(Chiron et al., 1992; Schoning & Hartig, 1996; Williams & Leggett, 1989)
	- Brain ^a	First increase, later decrease		
	- Other organs ^a	Increase		
	Carrier proteins		Neonates- children	(Johnson et al., 2006; Kanakoudi et al., 1995; Maharaj, Gonzalez, Cohen-Wolkowicz, Hornik, & Edginton, 2018; Sethi et al., 2016)
	- Albumin ^e	Increase	3 years of age	
- A1AGP ^e	Increase			
Hematocrit ^f	First decrease, later increase		(Fulgoni III et al., 2019; Jopling, Henry, Wiedmeier, & Christensen, 2009)	
Metabolism	Liver enzyme expression		Fetuses- children	(Bhatt et al., 2019; Divakaran, Hines, & McCarver, 2014; Johnson et al., 2006; Salem et al., 2014; Song et al., 2017; Upreti & Wahlstrom, 2016; Zaya, Hines, & Stevens, 2006)
	CYP1A2 ^c	Increase	2 years of age	
	CYP2B6 ^c	Increase		
	CYP2C8 ^c	Increase		
	CYP2C9 ^c	Increase		
	CYP2C19 ^c	Increase		
	CYP2D6 ^c	Increase		
	CYP2E1 ^c	Increase		
	CYP3A4 ^c	Increase		
	UGT1A1 ^c	Increase		
	UGT1A4 ^c	Increase		
	UGT1A6 ^c	Increase		
	UGT1A9 ^c	Increase		
	UGT2B7 ^c	Increase		
	UGT2B15 ^c	Increase		
	Hepatic transporter expression		Fetuses-adults	(Mooij et al., 2016; Prasad et al., 2016; van Groen et al., 2018)
	- Pgp ^c	Increase		
	- BCRP ^c	Stable		
	- MRP1 ^c	Increase		
	- MRP2 ^c	Stable/increase		
	- MRP3 ^c	Increase		
	- BSEP ^c	Stable/increase		
	- NTCP ^c	Increase		
- OATP-1B1 ^c	Stable			
- OATP-1B3 ^c	Stable/increase			
- OATP-2B1 ^c	Stable			
- OCT1 ^c	Increase			
Microsomal protein ^e	Increase	Neonates-adults	(Barter et al., 2008)	
Elimination	Glomerular filtration rate ^a	Increase	Fetuses-adults	(Hayton, 2000; Johnson et al., 2006; Piepsz, Tondeur, & Ham, 2006; Rhodin et al., 2009)
	Tubular transporter expression		Neonates-adults	(Cheung, van Groen, Spaans, et al., 2019)
	- Pgp ^c	Increase		

Table 1 (continued)

ADME process	Physiological parameter	Developmental pattern	Age range reported	Ref.
	- BCRP ^c	Stable		
	- MATE1 ^c	Stable		
	- MATE2-k ^c	Stable		
	- URAT1 ^c	Stable		
	- GLUT2 ^c	Stable		
	- OAT1 ^c	Increase		
	- OAT3 ^c	Increase		
	- OCT2 ^c	Increase		

Pgp, P-glycoprotein; BCRP, Breast cancer resistance protein; MRP, Multidrug resistance protein; OATP, Organic anion transporter protein; CYP, Cytochrome P450; A1AGP, Alpha-1-acid glycoprotein; UGT, Uridine diphosphate-glucuronyltransferase; BSEP, Bile salt export pump; Ntcp, Sodium-taurocholate cotransporting polypeptide; OCT, Organic cation transporter; MATE, Multidrug and toxin extrusion; URAT, Urate transporter; GLUT, Glucose transporter; OAT, Organic anion transporter.

^a Absolute length, volume, flow or rate.

^b mRNA expression.

^c Protein expression.

^d Percentage of body weight.

^e Concentration.

^f Percentage of blood volume.

Table 2

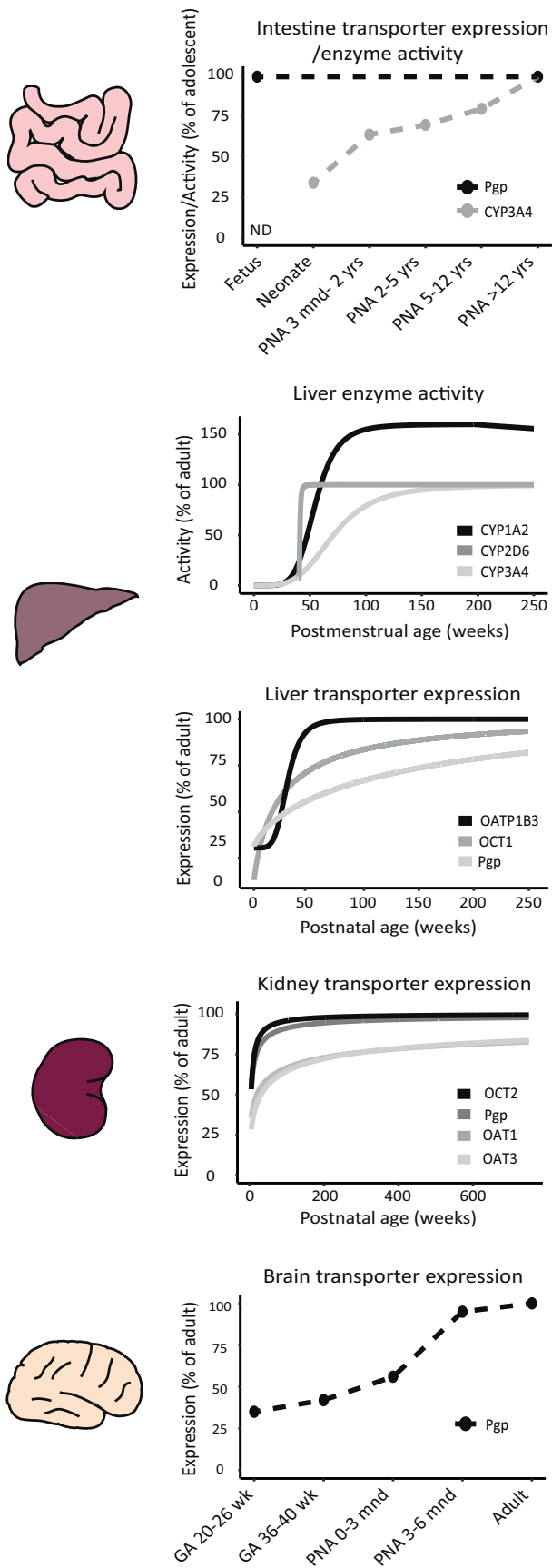
PBPK models including prediction of oral absorption.

Study	Parameter fitting/optimization needed?	Pediatric systems parameters included	Software used	Age range	Drug	Ref.
Parrott et al.	No	Gut size, intestinal transit time	Gastroplus®	Neonate, infant	Osetamivir	(Parrott et al., 2011)
Johnson et al.	Yes	GI tract size, CYP3A4 ontogeny	Simcyp®		Quetiapine	(Johnson et al., 2014)
Khalil et al.	Yes	Radius and length of intestinal segments, effective surface area intestinal sections, intestinal enzyme ontogeny	Simcyp® and PK-Sim®	11d–17.7y	Sotalol	(Khalil & Laer, 2014)
Willman et al.	Yes	Gastric emptying time, small and large intestinal transit time, effective surface area intestinal sections	PK-Sim®	0.5–18y	Rivaroxaban	(Willmann et al., 2014; Willmann et al., 2018)
Rasool et al.	Yes	Not stated	Simcyp®	0.12–19.3y	Carvedilol	(Rasool et al., 2015)
Cristofolletti et al.	Yes	Intestinal volumes, bile salt concentration, Gastric pH	Simcyp®		Fluconazole, Ketoconazole	(Cristofolletti et al., 2016)
Villiger et al.	Yes	Intestinal length, intestinal surface area, small intestinal transit time, fluid secretion volume	Gastroplus®	Newborns, infants, children	Sotalol, Paracetamol	(Villiger, Stillhart, Parrott, & Kuentz, 2016)
Moj et al.	Yes	Not stated	PK-Sim®	0–17y	Vorinostat	(Moj et al., 2017)
Kohlman et al.	No	Gut size and GI transit times	Gastroplus®	Newborns–adolescents	Carbamazepine	(Kohlmann et al., 2017)
Samant et al.	No	Not stated	Gastroplus®	0–22y	Desipramine	(Samant et al., 2017)
Johnson et al.	No	Gastric emptying, gastric and intestinal pH, intestinal length and diameter, intestinal transit time, salivary flow rates, gastric and intestinal volumes, intestinal bile salt concentration	Simcyp®	0–25y	Theophylline, Paracetamol, Ketoconazole	(Johnson, Bonner, et al., 2018)
Balbas-Martinez et al.	Yes	Not stated	PK-Sim®	3 m–12y	Ciprofloxacin	(Balbas-Martinez et al., 2019)

lower plasma albumin and alpha 1-acid glycoprotein concentrations compared to adults (Table 1), which is reflected in altered Kp values. These age-related changes may consequently result for a specific drug in a different predicted volume of distribution per kg body weight (Samant, Lukacova, & Schmidt, 2017).

Drug disposition into organs can also be described by diffusion-limited compartments. This mainly will be useful in cases where delayed drug penetration into organs is expected and/or transporter-mediated transfer of compounds across cell membranes needs to be accounted for. Data on maturation of drug transporters in the different organs are, however, limited and lagging behind the knowledge on the expression profiles of drug metabolizing enzymes (Table 1). Proof of principle for this approach was given in a study where OCT1-mediated liver uptake of morphine was included in a pediatric PBPK

model, which could be verified by comparison of predicted and measured clearance values (Emoto et al., 2018). Because morphine is a high extraction drug, clearance is mainly dependent on morphine delivery to the hepatocytes, which is influenced by hepatic blood flow and OCT1-mediated liver uptake, and to a lesser extent by UGT2B7 activity (Emoto, Johnson, Neuhoff, et al., 2018). First, OCT1 genotype was investigated as a source of variation in morphine liver uptake in adults and children older than 6 years of age (Emoto et al., 2017). Subsequently, ontogeny of OCT1 and an optimized relation between cardiac output and age, which influences hepatic blood flow, were included into the pediatric PBPK model to describe the clearance in neonates and young infants (Emoto et al., 2017; Emoto, Johnson, Neuhoff, et al., 2018). In a follow-up study, the ontogeny of UGT2B7 expression was also included in the modeling (Bhatt et al., 2019).



3.3. Metabolism

Most efforts have been directed at incorporating age-dependent changes in metabolic clearance into pediatric PBPK models (Fig. 2, Table 4). Data from *in vitro* assays (i.e. recombinant enzymes, human liver S9 fractions, human liver microsomes, or human hepatocytes) have been used to estimate hepatic clearance in adult models, which can also be applied to pediatric models by taking into account reported differences in enzyme expression/activity. Investigations on the expression ontogeny of hepatic CYP enzymes have resulted in accurate predictions for children down to an age of 1 month for drug metabolism covered by the enzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (Table 4) (W. Zhou et al., 2018). An *in vitro* study on the ontogeny profiles of different CYP enzyme activities, showed that for drugs handled by CYP1A2 and CYP3A4 these values resulted in an underestimation of the *in vivo* clearance in the pediatric age range (Johnson, Rostami-Hodjegan, & Tucker, 2006; Salem, Johnson, Abduljalil, Tucker, & Rostami-Hodjegan, 2014; Upreti & Wahlstrom, 2016). By using clinically determined clearance values of midazolam and sufentanil (both CYP3A4), theophylline and caffeine (both CYP1A2), the ontogeny for these enzymes was further refined (Salem et al., 2014). Subsequently, this was verified with clearance values for alfentanil (CYP3A4) and ropivacaine (CYP1A2) (Salem et al., 2014). A major drawback is that *in vivo* clearance data were obtained in ill children, which potentially has affected enzyme activity, but a good correlation between predicted and measured clearance values was found (Salem et al., 2014; Upreti & Wahlstrom, 2016). Although CYP enzyme developmental patterns are relatively well described, in several situations prediction of clearance was complicated by the absence of maturation profiles of metabolizing enzymes. Studies have been published describing models incorporating GST- and UGT-mediated clearance, in which only theoretical functions (i.e. not based on observed data) were used to describe enzyme ontogeny, for instance based on other isoenzymes or fitting to measured drug concentrations. While this indicates that prediction for these enzymes is more difficult, these efforts aid in further establishing their ontogeny profiles. (Diestelhorst et al., 2014; Jiang, Zhao, Barrett, Lesko, & Schmidt, 2013).

In neonatal and preterm models, measured drug concentration are less well predicted by PBPK models compared to older children and adults (Khalil & Laer, 2014; Templeton et al., 2018; T'Jollyn, Vermeulen, & Van Bocxlaer, 2018). Recently, developmental physiological parameters in the preterm/neonatal population were re-evaluated to provide a better mechanistic basis for this age group and drug plasma concentrations for six drugs were accurately described (Abduljalil, Pan, Pansari, Jamei, & Johnson, 2019a, 2019b). Another aspect considered specifically in neonates is that system-specific parameters can change rapidly over a relatively short period of time. In PBPK models parameters usually are fixed for a "virtual individual" during the time course of the simulation. However, to account for time varying physiology in neonates, in other words, to include growth and/or maturation in virtual individuals, a model has been developed in which the values for physiological parameters are re-defined during the time course of the (prolonged) simulation (Abduljalil, Jamei, Rostami-Hodjegan, &

Fig. 2. Developmental patterns in enzyme and transporter expression or activity in intestine, liver, kidney and brain. Solid lines indicate ontogeny profiles for which age-related equations are described. Dotted lines with point estimates indicate expression/activity levels at specific age groups. Refs: Intestine (Johnson et al., 2001; Konieczna et al., 2011), liver (enzymes) (Salem et al., 2014; Upreti & Wahlstrom, 2016), liver (transporters) (Prasad et al., 2016), kidney (Cheung, van Groen, Spaans, et al., 2019), brain (Lam et al., 2015). Pgp, P-glycoprotein; CYP, Cytochrome P450; OCT, Organic cation transporter; OAT, Organic anion transporter.

Table 3
PBPK models including prediction of drug distribution.

Study	Permeability-limited compartments included	Estimation method tissue-plasma partitioning coefficients (perfusion-limited compartments)	Software used	Age range	Drug	Ref.
Samant et al.	No	Lucacova	Gastroplus®	0–15 years	Desipramine	(Samant et al., 2017)
Emoto et al.	Liver	Rodgers and Rowland	Simcyp®	0–3 years	Morphine	(Emoto, Johnson, Neuhoff, et al., 2018)
Verscheijden et al.	Brain	Rodgers and Rowland	Rstudio®	0.25–15 years and adults	Paracetamol, naproxen, flurbiprofen, ibuprofen, meropenem	(Verscheijden et al., 2019)
Maharaj et al.	Brain	Rodgers and Rowland	PK-Sim®	0 years - adult	Lorazepam	(Maharaj et al., 2013)
Lukacova et al.	All tissues	Not applicable	Gastroplus®	11 days - 17 years and adults	Ganciclovir, valganciclovir	(Lukacova et al., 2016)

Table 4
PBPK models including prediction of metabolic elimination.

Study	Enzyme ontogeny	Software used	Age range	Drug	Ref.
Yun et al.	CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4	PK-Sim®	1 week - adult	Alfentanil, diclofenac, esomeprazole, itraconazole, lansoprazole, midazolam, ondansetron, sufentanil, theophylline, tramadol	(Yun & Edginton, 2019)
Zhou et al.	CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4	Simcyp®	1 month - adult	Theophylline, desloratidine, montelukast, diclofenac, esomeprazole, lansoprazole, tramadol, itraconazole, ondansetron, sufentanil	(W. Zhou et al., 2018)
Salem et al.	CYP1A2, CYP3A4	Simcyp®	1 day - adult	Caffeine, theophylline, midazolam, ropivacaine, alfentanil	(Salem et al., 2014)
Upreti and Wahlstrom	CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A	Simcyp®	1 day - adult	Caffeine, cotinine, nicotine, cyclophosphamide, methadone, phenytoin, tolbutamide, omeprazole, pantoprazole, propafenone, sevoflurane, sufentanil, midazolam, sildenafil, theophylline, S-warfarin, alfentanil, montelukast, efavirenz, lansoprazole, metronidazole, nevirapine, pantoprazole, ropivacaine	(Upreti & Wahlstrom, 2016)
Johnson et al.	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18/19, CYP2D6, CYP2E1, CYP3A4/5,	Simcyp®	1 day - adult	Midazolam, caffeine, diclofenac, omeprazole, cisapride, carbamazepine, theophylline, phenytoin, S-warfarin	(Johnson et al., 2006)
Edginton et al.	CYP1A2, CYP2E1, CYP3A, SULT, UGT1A1, UGT1A1, UGT1A6, UGT1A9, UGT2B7	PK-Sim®	1 day - adult	Paracetamol, alfentanil, morphine, theophylline, levofloxacin	(Edginton, Schmitt, & Willmann, 2006)
Bhatt et al.	UGT2B7	Simcyp®	1 day - adult	Morphine, zidovudine	(Bhatt et al., 2019)
Jiang et al.	CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, SULT, UGT1A1, UGT1A9, UGT2B15	Simcyp®	1 day - adult	Paracetamol	(Jiang et al., 2013)

Johnson, 2014). In this model, parameters involved in metabolic clearance e.g. CYP3A4 and CYP2C9 expression and liver weight were included, which resulted in better correlations between predicted and measured data for sildenafil (Abduljalil et al., 2014).

Finally, in case the relevant ontogeny profiles in children are robustly described in PBPK models, more complex age-related variation in drug metabolism may be detected. For example, a change in relative enzyme contribution during growth, as has been described for paracetamol and sirolimus, or a change in relative contribution of eliminating organs, as described for caffeine (Filler, 2007; Mooij et al., 2017; Pons et al., 1988).

3.4. Excretion

Renal excretion of drugs depends on (1) freely filtered drug that is determined by glomerular filtration rate and protein binding, (2) tubular secretion, and (3) tubular reabsorption. Equations describing ontogeny profiles for glomerular filtration rate (GFR) have been reported in multiple studies and used to estimate the amount of drug that is freely filtered (Duan et al., 2017; Johnson et al., 2006; Rhodin et al., 2009; Schwartz et al., 1976). In recently described models, GFR is predicted based on ontogeny functions derived from inulin and ⁵¹Cr-EDTA measurements, which gives more accurate results than using the creatinine clearance (Johnson et al., 2006; Rhodin et al., 2009). Inclusion of tubular secretion and absorption *via* transporter-mediated processes has

lagged behind in pediatric applications, as data on human membrane transporter ontogeny were, until recently, very scarce (Table 5, Fig. 2) (Cheung et al., 2019). By measuring the *in vivo* renal clearance of the P-glycoprotein substrate digoxin over a broad age range, the contribution of tubular secretion in children was used as a surrogate marker for the transporter's ontogeny profile (Willmann et al., 2014). This was done by subtracting the age-related GFR-mediated clearance from total digoxin clearance, which enabled simulation of rivaroxaban plasma concentrations (another P-glycoprotein substrate) over the pediatric age range. In this case the authors assumed that P-glycoprotein transport is the rate-limiting factor in tubular substrate secretion.

In case the transporter involved is unknown, or no transporter-specific substrate data is available to estimate transporter-mediated absorption or secretion, the ratio of $GFR_{\text{pediatric}}/GFR_{\text{adult}}$ has been used as a surrogate for pediatric renal clearance. However, this assumes that maturational processes in transporters are paralleling the development of GFR, which is often not the case (Cheung, van Groen, Spaans, et al., 2019; Duan et al., 2017; Johnson et al., 2006; Rhodin et al., 2009). The limitation of this assumption is also exemplified by a PBPK study in which this method was used to scale pediatric clearance for nine renally cleared drugs. Although for most children acceptable predictions were obtained, a trend towards an overestimation of renal clearance was found for children <2 years of age, indicating that physiological processes that affect renal clearance differ quantitatively between adults

and young children (W. Zhou et al., 2016). This might be explained by lower renal proximal tubular transporter expression of P-glycoprotein (apical), organic anion transporter (OAT)1, OAT3 and organic cation transporter (OCT)2 (basolateral) in neonates and young children (Cheung, van Groen, Spaans, et al., 2019). The largest overprediction of renal clearance was observed for vancomycin, which is transported by OCT2 (Sokol, 1991; W. Zhou et al., 2016). If urinary excretion of a drug is of minor influence on its total body clearance, ontogeny of renal clearance is often ignored in modeling (Walsh et al., 2016). Modeling the clearance of renally excreted drugs hence awaits inclusion of kidney transporter ontogeny and a means to scale *in vitro* to *in vivo* transport rates. A recent study indicates that this indeed leads to better predictions (Cheung et al., 2019). To our knowledge pediatric models including age-appropriate elimination *via* other routes such as bile, exhalation and sweat glands are not yet reported.

4. Exploratory pediatric PBPK models

4.1. Predictions of (target) tissue concentrations

Most PBPK models are used to describe plasma concentration-time profiles, but due to their compartmental structure, tissue concentrations can be predicted as well, which likely correlate better with the pharmacological/toxicological effects (Gerard et al., 2010; Hornik et al., 2017). Especially concentrations in brain are of interest, as this organ is protected by the blood-brain barrier equipped with multiple drug uptake and efflux transporters. For lipophilic drugs, relatively simple blood flow-limited models might be sufficient due to the rapid transfer of the drug into the brain and predictions can be done by calculating brain-plasma partitioning coefficients (Alqahtani & Kaddoumi, 2016; Donovan, Abduljalil, Cryan, Boylan, & Griffin, 2018). These models are not suitable for more polar drugs, where low BBB permeability restricts brain access resulting in low exposure levels and a lag-time between plasma and brain concentrations. One group started with a permeability-limited rat model that was adjusted for adult humans. This model was further refined to allow predictions on brain morphine extracellular fluid concentrations in children between 3 and 13 years of age (Ketharanathan et al., 2018; Yamamoto et al., 2017; Yamamoto et al., 2018). In another study, an adult PBPK-CSF model was extrapolated to children between 3 months and 15 years of age and verified with multiple drug CSF concentrations (Verscheijden, Koenderink, de Wildt, & Russel, 2019). Both groups did not specifically consider the influence of age on brain transporter expression, which is of main interest for further studies, as accumulating evidence indicates that at least P-glycoprotein activity appears age-related in the pediatric population (Nicolas & de Lange, 2019). Tissue concentrations in other organs have been described using simple K_p -based predictions, for example in skin, bone and lung (Hornik et al., 2017; Ogungbenro, Aarons, Cresim, & Epi, 2015; Thompson et al., 2019).

To date, models for the estimation of tissue concentrations have been more exploratory in nature as compared to models for predicting the course of the plasma drug concentration. This is due to limited access to tissue drug concentrations for verification, knowledge about disposition between different parts of an organ, and on organ transporter ontogeny. For a better applicability of these models, more studies are required to obtain mechanistic information on the processes that govern tissue exposure.

4.2. Prediction of fetal tissue concentrations

By linking fetal compartments to a maternal PBPK model, combined maternal and fetal ADME processes can be described. Maternal pregnancy-induced changes have been reported for volume of distribution, enzyme activity, blood flows, and plasma albumin and alpha-acid glycoprotein concentrations (Abduljalil, Furness, Johnson, Rostami-Hodjegan, & Soltani, 2012). For the fetal model, physiological

parameters and their developmental pattern are needed to predict drug exposure (Abduljalil, Jamei, & Johnson, 2019; Ke, Greupink, & Abduljalil, 2018). Recently, more data has become available for ontogeny of physiological parameters in the fetus, for instance concerning developmental patterns in organ volumes (Abduljalil, Jamei, et al., 2019; Abduljalil, Johnson, & Rostami-Hodjegan, 2018; Zhang et al., 2017).

Quantitative information on drug transfer from the maternal side to the fetal compartments can be obtained from clearance studies in the isolated perfused human placental cotyledon, or by measuring drug transfer over a cell line monolayer (De Sousa Mendes et al., 2017; Schalkwijk et al., 2018; Zhang et al., 2017; Zhang & Unadkat, 2017). Placental perfusion experiments are usually performed with normal term placentas, which means that transporter and enzyme expression are likely to be different at a lower gestational age, making extrapolation to earlier stages of pregnancy difficult. Experiments with cell line monolayers suffer from similar problems, as quantification of transporter expression is needed for the complete gestational age range to correct for the differences in abundance between fetal placenta and the cell system used for predictions (Ke et al., 2018). In addition, parameter optimization and model verification are challenging as for obvious reasons fetal drug exposure data at an early gestational age may be hard to acquire. Model verification of fetal compartments with cord blood is an important source of data, although samples are only available at birth and differences in timing between the last dose and sampling introduces variability in the concentrations measured. Also single measurements do not give information on the underlying fetal concentration-time profiles (Schalkwijk et al., 2018).

4.3. Predictions for monoclonal antibodies

Therapeutic use of monoclonal antibodies (mAbs) and large protein molecules has grown rapidly over the years. Although their body disposition is rather different from that of small molecule drugs, PBPK models can also be valuable in predicting the pharmacokinetics of biologicals (Gill, Gardner, Li, & Jamei, 2016). Models for mAbs require incorporation of different physiological processes, compared to small molecules, such as lysosomal degradation, lymph flows, endogenous antibody concentrations, and FcRn receptor-mediated recycling, which also show age-related variation (Edlund, Melin, Parra-Guillen, & Kloft, 2015; Jones, Mayawala, & Poulin, 2013; Malik & Edginton, 2018). Data is not yet available for all processes affecting pharmacokinetics of mAbs, which underscores the need for studies unraveling these developmental physiological parameters. Nevertheless, an attempt was made to scale an adult PBPK model to a pediatric variant for the therapeutic monoclonal IgG antibodies bevacizumab and palivizumab and although many parameters were uncertain, this approach can be used as a framework for building a generic pediatric PBPK model that captures all complexities (Hardiansyah & Ng, 2018).

4.4. Determine effects of non-maturational factors

In addition to age-related variation in ADME processes, PBPK models are very well suited to explore and/or incorporate the effect of non-maturational factors, such as disease, genetics and drug-drug interactions (DDIs) on pharmacokinetics (Zakaria & Badhan, 2018). For example, depending on the maturation profiles of the proteins involved in a DDI, the magnitude of interaction may be different in various age groups, which indicates that information on enzyme/transporter protein ontogeny, and their effects on the interaction needs to be described (Salem, Johnson, Barter, Leeder, & Rostami-Hodjegan, 2013). Simulations of DDIs are not yet common practice in pediatric populations, although some papers have been published, mainly on CYP3A4 (A. Li, Yeo, Welty, & Rong, 2018; Ogungbenro, Aarons, & Cresim, & Epi, C. P. G., 2015; Olafuyi, Coleman, & Badhan, 2017). In these studies, no verification was performed in children < 2y of age, in which developmental differences in CYP3A4 expression are expected to have the largest

Table 5
PBPK models including prediction of renal elimination.

Study	GFR ontogeny	Tubular secretion/absorption ontogeny	Software used	Age range	Drug	Ref.
Balbas-Martinez	Rhodin ontogeny	p-Aminohippuric acid ontogeny	PK-Sim®	3 m-12y	Ciprofloxacin	(Balbas-Martinez et al., 2019)
Lukacova et al.	PEAR module ontogeny	Optimized to measured data Adult transporter expression levels	Gastroplus®	11 days – 17 years and adults	Ganciclovir, valganciclovir	(Lukacova et al., 2016)
Zhou et al.	Johnson ontogeny	Same as GFR ontogeny	Simcyp®	Neonates- adults	Nine renally cleared drugs	(W. Zhou et al., 2016)
Walsh et al.	NA	NA	Simcyp®	0–12 months and adults	Actinomycin D	(Walsh et al., 2016)
Parrott et al.	1/10th of adult	1/10th of adult	Gastroplus®	Neonates, young infants, adults	Oseltamivir	(Parrott et al., 2011)
Duan et al.	Johnson ontogeny	Same as GFR ontogeny	Simcyp®	1 day – 17 years	Linezolid, emtricitabine	(Duan et al., 2017)
Willmann et al.	Rhodin ontogeny	Digoxin tubular secretion (P-glycoprotein) ontogeny	PK-Sim®	Neonates-adolescents	Rivaroxaban	(Willmann et al., 2014)
Cheung et al.	Not stated	Kidney developmental drug transporter expression data	Not stated	0–7 years and adults	Tazobactam	(Cheung, van Groen, Burckart, et al., 2019)

impact on the difference in DDI magnitude compared to adults. Disease effects have been incorporated in adult models for patients with impaired kidney (Yee et al., 2017; L. Zhou et al., 2019) and liver function (Rhee et al., 2017), but inclusion in pediatric models is hampered by the lack of quantitative data on the pathophysiological processes (G. F. Li, Gu, Yu, Zhao, & Zheng, 2016; Rasool et al., 2015; Watt et al., 2018). This is also seen in studies where the effects of a reduction in blood flow were investigated, which at this stage could not be mechanistically included, because of pathophysiological differences in organ blood flow in children compared to adults (Emoto, Johnson, McPhail, et al., 2018; Rasool, Khalil, & Laer, 2016). Effects of genetic polymorphisms have been studied in pediatric PBPK models, often associated with changes in metabolizing enzyme activity (Ogungbenro & Aarons, 2015; Zakaria & Badhan, 2018). Similarly, genetic variation in transporters and target receptors can be incorporated (Hahn et al., 2018). If more physiological data about specific patient groups becomes available, better individualized PBPK model predictions can be made allowing subclassification within age groups, thereby reducing unexplained inter-individual variability and paving the way for more individualized modeling.

4.5. PBPK-PD models

Determination of PD differences between adults and children is of major importance to allow pediatric bridging studies for drugs in development. Introducing the relevant pharmacodynamic processes into pediatric PBPK models will be the next step to determine fully age-appropriate drug doses. The structure of many different PBPK models developed so far is relatively uniform, however, pharmacodynamic modules have their unique structure that is dependent on available knowledge and the process that is being described. Most straightforward is to compare drug concentrations with target thresholds in case of antibiotics, although in a more complex model bacterial count over time could be described (Mohamed, Nielsen, Cars, & Friberg, 2012; Thompson et al., 2019). There are relatively few examples of models that have incorporated a more complex pharmacodynamic component for adults and children (Kechagia, Kalantzi, & Dokoumetzidis, 2015; Kuepfer et al., 2016; Moj et al., 2017; Smith, Hinderliter, Timchalk, Bartels, & Poet, 2014). An important aspect for future model development will be the inclusion of age-related drug effects instead of connecting an adult pharmacodynamic model to a pediatric pharmacokinetic component, for which more developmental *ex vivo* and clinical research is clearly needed (Marshall & Kearns, 1999).

5. Physiologically-based toxicokinetic models

The same principles for building a PBPK model are also applied when assessing the kinetics of a toxic compound, referred to as physiologically-based toxicokinetic (PBTk) models. In fact, the physiologically-based kinetic modeling approach has been around in toxicology longer than in the field of pharmacology (Pelekis, Gephart, & Lerman, 2001). These type of models are usually developed for different animal species and subsequently translated to humans to predict internal exposure as part of the risk assessment of a wider range of chemicals, like pollutants (Emond, Ruiz, & Mumtaz, 2017; Tohon, Valcke, & Haddad, 2019), metals (Fierens et al., 2016; Kirman, Suh, Proctor, & Hays, 2017), pesticides (Lu, Holbrook, & Andres, 2010; Oerlemans et al., 2019) and industrial products (Edginton & Ritter, 2009). Children have also been considered as a vulnerable group at risk, as they may experience relatively higher exposures to chemicals and/or be more sensitive to harmful effects. For example, a higher exposure to bisphenol A was predicted in children, because of their lower elimination capacity compared to adults and the potentially higher weight-normalized intake (Edginton & Ritter, 2009). A difficulty encountered while predicting developmental toxicity is that compared to PBPK models, human and particularly pediatric PBTk models often will carry more uncertainty about the dose internalized, and hence higher variability in predictions (Lu et al., 2010).

6. Quality control

The widespread adoption of PBPK modeling in pediatric drug development and personalized dosing, largely depends on the quality of the models and their validity to accurately predict exposure. The variety in claims made by authors on reliability of the model predictions can be explained by differences in quality and certainty of model parameter estimates. Confidence in modeling results could be increased by performing simulation with similar drugs/formulations (Johnson, Zhou, & Bui, 2014), or the ability to predict drug-drug interactions (Ogungbenro et al., 2015).

Assessing the quality of PBPK models is a complicated task due to the wide variety of different purposes for model use, difference in (mechanistic) complexity, the number of data that is available for building and verification, and heterogeneity in quality measures (Sager et al., 2015). For pediatric PBPK models this might be even more difficult as also developmental processes need to be incorporated and validated. Depending on the purpose of the PBPK model, its quality needs to be evaluated accordingly. In case a model is designed to replace clinical studies in children, confidence in model performance ideally should be high and

parameter uncertainty low, whereas for exploring mechanistic hypotheses (e.g. age-related differences in ontogeny), a lower level of confidence in less essential parameters could be acceptable (EMA, 2016). To have more insight into model quality, the following key aspects need to be considered while evaluating PBPK models.

6.1. Mechanistic uncertainty

Uncertainty in the mechanistic bases of the model increases the prediction error, while translating processes affecting absorption, distribution and elimination from adults to children. For example, the contribution of different enzymes involved in drug metabolism can be unknown, or disease-mediated changes on physiological processes are not quantitatively described (Johnson, Cleary, et al., 2018). This means that assumptions are required, of which the impact on model outcomes needs to be evaluated by sensitivity analysis.

6.2. Scaling/fitting parameters

If (multiple) parameters are scaled, uncertainties in other parameters could be masked or compensated in case they are not uniquely identifiable. Apparently acceptable concentration-time profiles produced by a model for one drug or (pediatric) population, will in this case not be reproducible for another drug or in another population (Calvier et al., 2018). Ideally, external datasets are needed to confirm the validity of the scaled parameter in a learning-confirming cycle. As a minimum requirement, biological plausibility of the scaled parameter could be evaluated.

6.3. Quality and quantity of in vivo data for verification

The number and quality of data for verification is variable, ranging from sparse or opportunistic data to dense clinical trial data. Models are generally accepted when they correlate to observed data even if they are sparse, although the latter requires extra caution if for example a measured concentration-time profile is not available for comparison with simulated data (Sager et al., 2015).

6.4. Software package

Multiple software programs are used for modeling and some can be considered better validated, as they have been tested and employed by a large number of users. Currently available commercial software programs for pediatric PBPK modeling include Gastroplus, Simcyp and PK-Sim. Gastroplus has historically focused on prediction of drug absorption, and Simcyp is often used for prediction of DDI's, although areas of application have been extended. The open access software platform PK-Sim is another option for which no coding skills are required. Manually coded models are more prone to errors even after review, but may be more flexible in order to answer specific research questions.

6.5. Transparency

To gain insight into parameter certainty, ideally an overview of the model parameters (drug-related as well as physiological parameters) is described along with the references from which they originated.

7. Regulatory applications

Because physiological and drug-specific parameters are included separately, PBPK models are suited to predict drug concentrations in a population, or for applications where extensive clinical pharmacokinetic information is not yet available. Currently, of all PBPK models used in drug approval applications submitted to the FDA about 15% serve a pediatric purpose, which is more than seen for other "special populations" like elderly, or patients with impaired renal or hepatic

function (Grimstein et al., 2019; Jamei, 2016). PBPK modeling in general, and pediatric PBPK modeling in particular, is a relatively new discipline, but its application is increasing rapidly in the majority of pharmaceutical companies. Examples are now available where clinical studies have been replaced or informed by pediatric PBPK simulation efforts (Shebley et al., 2018; Wagner et al., 2015). For example, models have been used to (1) set a starting dose in a clinical trial with eribulin in children and adolescents 6–18 years of age, (2) bridge from immediate release to extended release quetiapine formulations in children and adolescents 10–17 years of age, and (3) inform deflazacort dose adjustments needed when given together with drugs that may cause interactions in children and adolescents 4–16 years of age (FDA, 2016; Johnson et al., 2014; Shebley et al., 2018). Regulatory authorities have recognized the potential of PBPK modeling and guidelines were issued mainly focused on what information should be incorporated in the PBPK model documentation by pharmaceutical industry, which might further standardize the process of model development in regulatory applications (EMA, 2016; FDA, 2018).

8. Future perspectives

PBPK modeling in children aids in predicting the pediatric pharmacokinetics of drugs for which no or sparse data is available. Whereas model performance is currently more challenging for neonatal populations, drugs metabolized by non-CYP enzymes, drug transporter substrates, and drugs which are orally absorbed, PBPK models are continuously improved and refined in a learn-and-confirm cycle by the inclusion of more accurate model parameters.

One aspect that could further improve pediatric PBPK model development is to fill the gap in availability and quality of systems data. For this purpose, quantitative proteomics is an attractive technique to assess ontogeny patterns for absolute expression of drug metabolizing enzymes and transporters in different organs and the interplay with other co-variables. This approach is especially suitable for pediatric populations where a low number or size of samples is usually available. As multiple proteins can be quantified at the same time, correlation between protein expression can also be considered (Achour, Barber, & Rostami-Hodjegan, 2014; Heikkinen, Lignet, Cutler, & Parrott, 2015). The number of studies in children is limited, pediatric PBPK modeling therefore will require pooling of data, resources and knowledge. This also includes combining tissue material, plasma and body fluid samples from different institutions and biobanks to cover the full age range of pediatric development.

In addition to obtaining better defined physiological parameters, there is a need for verification of models. Opportunistic sampling of plasma and other body fluids or tissues would be a way to obtain measurements for drugs already on the market, which were not thoroughly investigated previously (Hahn et al., 2019; Salerno, Burckart, Huang, & Gonzalez, 2019). Open access publishing and publication of raw data will aid in making optimal use of already available clinical data. If it is still not possible to obtain enough data, micro-dosing studies could provide a good alternative, as long as saturation of enzymes and transporters is not expected at therapeutic doses. By administering a small amount of a labeled drug (often 1/100 of usual dose) its pharmacokinetics can be determined, without the risks associated with potential toxic effects (Mooij et al., 2017; Roth-Cline & Nelson, 2015). From a modeling perspective, good quality clinical data is extremely valuable for studying the ontogeny of system parameters in case biological samples are hard to obtain (e.g. blood brain barrier transporter expression).

Whereas in the coming years pediatric PBPK model improvement will be focused on prediction in specific age groups and for children having co-morbidities by better capturing the underlying (patho)physiological parameters, an area of potential future benefit is the use of PBPK modeling in personalized medicine. This will require even more detailed information on demographic, genotypic, and phenotypic characteristics. Development of a "virtual twin" in which patient-specific

features like, age, weight, height, gender, ethnicity, and genetics of drug metabolizing enzymes/transporters are taken into account in PBPK models, will contribute to better personalized dosing and predictions within specific age groups. This will allow pediatric PBPK models to find their way into clinical practice (Tucker, 2017).

9. Conclusion

The application of pediatric PBPK models have gained momentum over the last years, partly because their development has been stimulated by the increased interest of regulatory authorities in this “special population” and the obligation of investigating pharmacological differences between children and adults. Different pediatric PBPK models have been developed for a wide variety of purposes, including substitution of clinical studies. While uncertainty in some physiological parameters is higher and less data might be available for model verification in children, pediatric PBPK models have become more robust and start to approach the mechanistic basis seen in their adult counterparts. In the coming years model quality and mechanistic basis will further improve by inclusion of more (reliable) physiological data, which will provide a sound basis for pediatric model acceptance (Burckart & van den Anker, 2019). In this way, with concerted efforts of academia, PBPK model developers, industry and regulators, the use of this approach will further expand and be applied to optimize drug development in the pediatric population. The role of modeling and simulation in drug development will undoubtedly increase and particular effort should be invested in the development of these models for children, to exploit the enormous potential of this evolution also for the pediatric population.

Declaration of Competing Interest

TNJ is an employee of Certara UK Limited and involved in the development of the commercial Simcyp PBPK model. LFMV, JBK, SNW and FGMR declare that there are no conflicts of interest.

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