Citation: Clin Transl Sci (2021) 14, 29–35; doi:10.1111/cts.12843

REVIEW

Pediatric Pharmacokinetics and Dose Predictions: A Report of a Satellite Meeting to the 10th Juvenile Toxicity Symposium

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On April 24, 2019, a symposium on *Pediatric Pharmacokinetics and Dose Predictions* was held as a satellite meeting to the 10th Juvenile Toxicity Symposium. This symposium brought together scientists from academia, industry, and clinical research organizations with the aim to update each other on the current knowledge on pediatric drug development. Through more knowledge on specific ontogeny profiles of drug metabolism and transporter proteins, integrated into physiologically-based pharmacokinetic (PBPK) models, we have gained a more integrated understanding of age-related differences in pharmacokinetics (PKs), Relevant examples were presented during the meeting. PBPK may be considered the gold standard for pediatric PK prediction, but still it is important to know that simpler methods, such as allometry, allometry combined with maturation function, functions based on the elimination pathway, or linear models, also perform well, depending on the age range or the mechanisms involved. Knowledge from different methods and information sources should be combined (e.g., microdosing can reveal early read-out of age-related differences in exposure), and such results can be a value to verify models. To further establish best practices for dose setting in pediatrics, more *in vitro* and *in vivo* research is needed on aspects such as age-related changes in the exposure-response relationship and the impact of disease on PK. New information coupled with the refining of model-based drug development approaches will allow faster targeting of intended age groups and allow more efficient design of pediatric clinical trials.

The disposition of drugs in children differs widely from that in adults due to developmental changes in the biological processes involved.[1] Understanding the ontogeny of these processes, such as drug metabolism and drug transport, aids in the prediction of pharmacokinetics (PKs) in children, and subsequently in developing pediatric dosing regimens. In recent years, our knowledge on the ontogeny of processes involved in drug disposition has rapidly increased. This information can be incorporated in pediatric physiologically-based PK (PBPK) models, which take into account age-specific physiological parameters and disease state of the patient, as well as compound-specific data, such as physicochemical properties and intrinsic metabolic rates. Hence, the reliability of a pediatric PBPK model depends highly on the underlying ontogeny data. Furthermore, approaches such as allometric scaling and population pharmacokinetic (Pop-PK) modeling are increasingly used to determine or predict a pediatric drug dosing regimen. Differences among allometric scaling, Pop-PK modeling, and PBPK modeling are outlined in **Table 1**.

On April 24, 2019, a symposium on *Pediatric Pharmacokinetics and Dose Predictions* was held as a satellite meeting to the 10th Juvenile Toxicity Symposium at Janssen in Beerse, Belgium. This symposium brought together scientists from academia, industry, and clinical research organizations with the aim to update each other on the current knowledge on pediatric drug development. Moreover, the participants pinpointed knowledge gaps and areas for future practice and research. This mini-review summarizes the presentations given and the ensuing discussions.

UPDATES ON ONTOGENY INFORMATION INVOLVED IN DRUG DISPOSITION

Drug metabolizing enzymes and transporters are important determinants of drug disposition. Age-related changes in their expressions and functional activity levels play a major role in drug disposition; hence, are key determinants of PK, toxicity, and safety of many drugs prescribed to children. Over the years, ontogeny data on drug metabolizing

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Received: May 19, 2020; accepted: June 14, 2020. doi:10.1111/cts.12843

Table 1 Comparison of model-based approaches in extrapolating the adult PK to pediatrics

Methods	Allometric scaling	Pop-PK	PBPK
Characteristics	Empirically derived function, predicting single PK parameters (typically CL, V) based on demographic information (typically BW). (e.g., k = 0.75 for CL, 1.0 for V)	Estimation: PK parameters estimated to describe data (retrospective) and covariates found *post hoc*. Prediction: based on descriptive model and allometric or maturation function predictions for the current population within the dose range studied and/or extrapolations for other doses and/or other age ranges (prospective)	Mechanistically predict PK based on interplay between drug-specific characteristics (logP, MW, pKa, enzyme kinetics, etc.) and organism anatomy/physiology information
Main application	Used to extrapolate specific PK parameters or for fitting as part of Pop-PK or PBPK model	Systematic, statistically driven PK/covariate analysis for specific compounds	Provide "the whole picture" of different population characteristics and growth and maturation aspects
Strength	Simple and fast. Minimal resources (no model building)	Can integrate complex customized allometric and maturation functions. Can integrate PK, PD (biomarker, efficacy, safety) and disease progression.	Can be used for predictions with no/little clinical information. Can leverage physiology/ontogeny information to predict PK in younger age groups. Outputs whole-profile predictions for different organs/tissues.
Limitations	Only capture body size related information. Scaling of isolated aspect of PK—no representation of, for example, maturation of metabolic enzymes, distribution, shape of PK, etc. Promising in cases of straight-forward PK that is determined by few, well understood parameters. Scientifically always inferior when compared to Pop-PK and PBPK.	Knowledge about the appropriate allometric and maturation functions required. Predictions limited to scaling of selected parameters within the population and doses studied—more narrow focus vs. PBPK software (unless full-body PBPK). Typically, rich physiological information is not applied for extrapolations.	Ideally, enzyme/transporter information and other drug-specific parameters required (not always available). Not all models have open science. *In vitro*/*in vivo* quantitative information often required for model refinement and verification.

BW, body weight; CL, clearance; logP, lipophilicity partition coefficient; MW, molecular weight; PBPK, physiologically-based pharmacokinetics; PD, pharmacodynamic; PK, pharmacokinetic; pKa, acid dissociation constant; Pop-PK, population pharmacokinetic modeling; V, distribution volume.

enzymes and transporters has become available in literature, on which updates are given below.

Age-dependent changes in phase II drug metabolizing enzyme activity

Historically, ontogeny of phase II drug metabolizing enzymes UDP-glucuronosyltransferase (UGT) enzyme activity has been less studied than ontogeny of phase I metabolism by the CYP450 superfamily. Recently, glucuronidation activity of multiple UGT isoforms was simultaneously studied using human liver microsomes, after optimal methodological conditions had been defined to minimize experimental variability.

An automated ultra-high performance liquid chromatography tandem mass spectrometry-based UGT profiling assay was developed and optimized to assess simultaneously the glucuronidation activity of 10 hepatic UGT isoforms using a cocktail incubation approach in human liver microsomes.[2] Hepatic glucuronidation activity of hepatic UGT isoforms was determined under similar optimized experimental conditions, including tris-HCl buffer (100 mM at pH 7.4), 10 mM magnesium chloride, 5 mM UDP glucuronic acid, and no bovine serum albumin supplementation. This approach enabled a more effective performance of multidonor UGT activity studies, including correlation analysis of UGT activities using multiple donors, and assessment of ontogeny in UGT-mediated drug clearance.

In agreement with previous literature, UGT1A4, UGT1A6, and UGT2B17 activities were found to increase from infant age to adulthood.[3] UGT2B17 increased slowly, with adult levels reached at adolescence. In contrast, maturation of UGT1A1, UGT1A9, UGT2B7, and UGT2B15 differed from published data. Limited age-dependent changes were found only for UGT1A3, UGT2B4, and UGT2B10 activity, the ontogeny of which had not been described previously.

Age-dependent changes in transporter expression

Recent advancements in protein expression methods enabled the use of liquid chromatography tandem mass spectrometry to quantify multiple transporters at once in a very limited sample volume, which is favorable for pediatric studies where tissue is scarce and limited in volume. Recent studies using pediatric intestine,[4] liver,[5] and kidneys,[6] tissue have added to the knowledge gained in previous gene expression and immunohistochemistry studies. These new data may be used as surrogate parameters for functional activity, as activity studies are challenging or even not feasible in pediatric tissue. The lack of validated markers to study transporter activity *in vivo*, further hampers activity studies in children.[7]

The key observations from the *ex vivo* studies in intestine,[4] liver,[5] and kidneys[6] were that most clinically relevant transporters, including multidrug resistance protein 1, organic anion transporting (OAT) polypeptide 1B1, and bile salt export pump, displayed an age-dependent ontogeny pattern. This pattern would suggest that the clearance of exogenous and endogenous substrates for these transporters could be subject to age-related changes. The ontogeny profiles were

transporter-isoform-dependent and organ-dependent. The latter property was exemplified by the maturation rate of hepatic multidrug resistance protein 1 in the liver, which reached no more than 50% of adult expression levels at 2.9 years of age, whereas by that age full adult levels were achieved in the kidneys. Interestingly, within the pediatric cohorts, correlations between the expression levels of various transporters were detected, for example, for organic anion transporter (OAT)1 and OAT3 in the kidneys. This is not surprising, as OAT1 and OAT3 are located in adjacent regions on chromosome 11 and are both regulated by the transcription factors hepatocyte nuclear factor 1α and 1β. The detailed ontogeny profiles of these and other transporters can be found in the original publications.[4–6]

Literature review on the ontogeny of hepatic drug metabolism and drug transport across species

As pediatric samples are scarcely available, information from single papers is limited and fragmented. For the liver in particular, available reviews are based on qualitative description of ontogeny profiles and include very few data on nonclinical species. Therefore, as part of the Health and Environmental Sciences Institute multisector collaborative research effort,[8] the ontogeny of hepatic drug metabolism and drug transport is currently quantitatively reviewed, aiming to create high-resolution ontogeny profiles of drug metabolizing enzymes and transporters for human and nonclinical species.

In short, various developmental patterns for drug transporter and drug metabolizing enzyme isoforms could be constructed, which were classified as increasing, decreasing, or stable expression/activity as a function of age. The acquired ontogeny profiles will be available for integration in *in vitro-in vivo* extrapolation algorithms linked with PBPK modeling, to improve prediction of hepatic drug disposition in pediatric populations. In addition, insights into the ontogeny profiles of the corresponding hepatic drug metabolizing enzymes and transporters in nonclinical species may help select the appropriate juvenile animal model(s) for drug safety evaluation.

MODELING AND SIMULATION IN PEDIATRIC DOSE SELECTION

Use of pediatric PK prediction in current practice

Recent years have seen a resurgence in the use of Pop-PK, PBPK models, and simulation for pediatric PK prediction, especially where they can replace clinical studies and where designing such studies is more challenging. More specifically for drug development, recent regulatory guidelines[9] have set out a framework defining the required software qualification and model predictive performance verification for the use of virtual trials in lieu of clinical studies based on regulatory decision impact.

Case examples of pediatric PK prediction in drug development

The four cases below show how Pop-PK and PBPK approaches aid in pediatric PK prediction.

Case study 1: Prediction of pediatric drug-drug interactions. The glucocorticoid deflazacort is converted to active 21-desacetyl deflazacort by esterases, and is further eliminated by cytochrome P450 (CYP) 3A4. In adults, a PBPK model was developed and verified to predict concentration-time profiles and drug-drug interactions with the CYP3A4 inhibitors (clarithromycin and fluconazole) and inducers (rifampicin and efavirenz). The model was further verified in children 4–11 years old and in adolescents 12–18 years old and was able to capture the concentration-time profiles and variability with 80% of individual observed data with the 5th and 95th percentiles of the simulation. The predicted area under the curve (AUC) ratios following co-administration of the four interacting drugs were not significantly different among adults, adolescents, and children. This information was accepted by the US Food and Drug Administration (FDA) as it supported similar dosage adjustments for deflazacort in children and adults administered the interacting drugs, and prevented the need for further clinical studies.[10]

Case study 2: Pediatric PBPK predictions incorporating disease effects. Drug X was being further developed to treat sickle cell disease (SCD) in children, and clinical data from healthy adults and adults with SCD were available. In healthy adults, the drug in question had low clearance with 74% of metabolism by CYP3A4, 19% by reduction, and 8% by UGT. It had very high plasma protein binding (fraction unbound (f_u) = 0.002) and a high blood-to-plasma ratio of 33. Disease-related hypoalbuminemia resulted in a higher f_u and a lower hematocrit, thereby resulting in a lower blood-to-plasma ratio of 15.5. The concentration-time profiles following single and multiple doses were successfully predicted in healthy adults, followed by adult with SCDs (90% individual observed data within 5th and 95th percentiles of predicted). The ontogeny of CYP3A4 was included in the pediatric model.[11,12] Predictions in children 6 to < 12 years old with SCD again showed close agreement with observed data. Final predicted doses down to a 9-month to 2-year age group were based on those resulting in the equivalent exposure (AUC_{0-tau}) following a 900 mg dose in adults. These predicted doses are currently being evaluated in a pediatric clinical trial.

Case study 3: Extrapolation of quetiapine extended release formulation from adults to pediatrics. A dose for an extended release formulation in children was set, without having performed an additional clinical trial, based on existing preclinical and clinical exposure data.[13] A PBPK modeling approach was used to bridge the formulations between adults and pediatric subjects (see **Figure 1**). The PBPK model was able to recapitulate the clinical data of immediate release formulation in adults and adolescents. It was predicted that children and adolescents are likely to achieve a similar exposure following administration of either the extended release or immediate release formulations at similar total daily doses. This analysis was accepted by the regulatory agencies.[10]

Case study 4: PBPK modeling to propose starting dose and dosing regimen in phase II trials. Compound "ROX" is a low clearance compound, a CYP3A and CYP2C8 substrate *in vitro*, and a Biopharmaceutics Classification System class II compound, which is under development for the treatment of

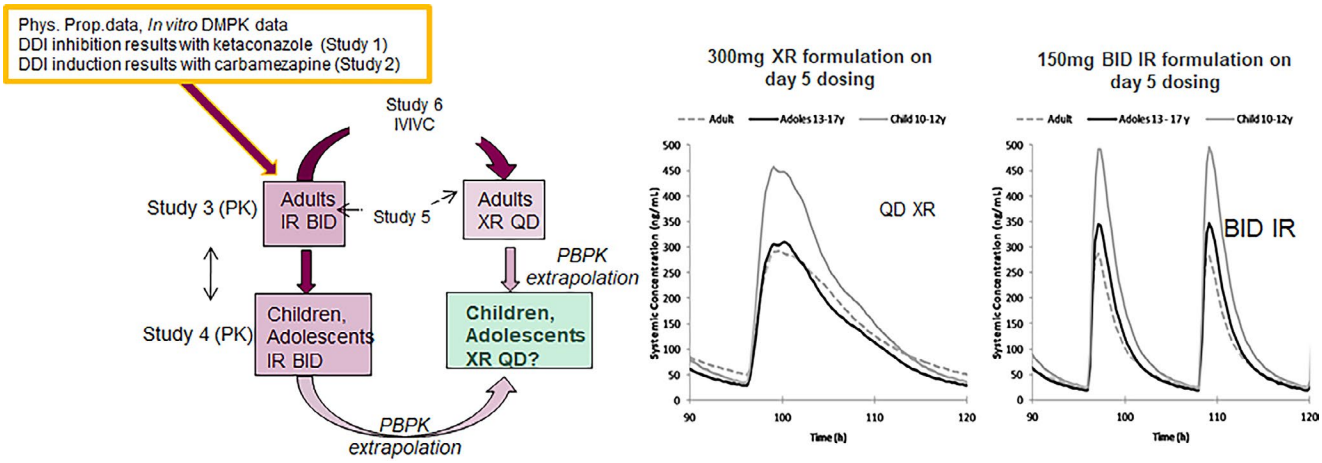

Figure 1 The physiologically-based pharmacokinetic (PBPK) modeling approach was successfully utilized to bridge the formulations between adults and pediatric subjects. Clinical data of immediate release (IR) formulation available for adults, adolescents and children (10–12 years), but extended release (XR) formulation data was available only for adults. PBPK model-based extrapolation was used to inform the dosing regimen for XR in children and adolescents. For details see Johnson *et al*.[13] DDI, drug-drug interaction; DMPK, drug metabolism and pharmacokinetics; IVIVC, *in vitro* to *in vivo* correlation; PK, pharmacokinetic.

central nervous system disorders in both adults and children. To achieve similar exposures in these age groups based on AUC, starting doses and dosing algorithms for pediatric trials in patients 5–17 years old were predicted using a PBPK approach. The model development followed a learn-and-confirm approach, starting from *in vitro* and *in vivo* data from the preclinical development followed by refining of the model once human adult data became available.

The model was able to describe very well the phase I studies (single ascending dose, multiple ascending doses, and food effects), generating confidence on its use to propose the pediatric starting doses and dosing algorithms. As part of the dosing algorithm, an age binning criterium for the upcoming ROX phase II study in pediatrics was proposed and included in the study design. The final pediatric dose selection will be confirmed with a mixture of PBPK and Pop-PK modeling. This work highlights the utility of using PBPK to inform clinical study design in the pediatric population in early drug development.

Strategies to scale pediatric drug clearance

Pediatric dose prediction using PBPK modeling can be time-consuming and requires all parameters to be known, which may not always be the case. As a result, allometric (0.75 weight-based scaling) or linear scaling for dose predictions or adjustments in pediatrics has always been attractive and has generally been accepted for older age ranges, such as adolescents. An important question is until what age and for what drugs these approaches can be used. A systematic performance evaluation of these methods was carried out based on a pediatric PBPK workflow.[14,15]

The findings showed that allometric scaling, which solely requires information on bodyweight, can be used disregarding the drug properties and the routes of drug elimination for scaling clearance from adults to children as young as 5 years of age. Below this age of 5 years, for hepatically cleared drugs, linear scaling was found to be reasonably accurate down to the age of 2 years, except for alpha-1-acid glycoprotein (AGP)-bound drugs with a low extraction ratio and mature isoenzymes.[15] When allometric scaling is combined with information of maturation of isoenzymes and microsomal protein per gram of liver, hepatic metabolic clearance for all low and intermediate extraction ratio drugs can be predicted with reasonable accuracy in all cases, except for drugs binding to AGP in neonates.[16] For drugs with a high extraction ratio in adults, PBPK modeling is the best approach in this age range.

Besides allometric or linear scaling, extrapolation on the basis of the main elimination pathway of the concerned drug is also often proposed. A systematic evaluation of scaling between hepatically cleared drugs sharing the main elimination pathway revealed that between-drug extrapolation of pediatric covariate functions can be applied to low and intermediate extraction ratio drugs eliminated by one isoenzyme and binding to human serum albumin in children > 1 month old.[17] For drugs undergoing glomerular filtration, linear scaling can be used in children as young as 1 month of age, except for drugs highly bound to AGP (i.e., with an f_u in adults < 0.34).[15] In term neonates, linear scaling was found to outperform allometric scaling for human serum albumin and AGP-bound drugs excreted through glomerular filtration.[15]

CLINICAL PERSPECTIVES AND APPROACHES

Approaches to improve drug dosing and drug development in neonates

Neonatal clinical pharmacology is faced with an extensive inter-individual and intra-individual variability in drug exposure. Besides these maturational covariates, the various impacts of diseases, co-medication, and treatment modalities need to be taken into account.[18,19] Once the main drivers of drug disposition have been explored, these covariates can be implemented in PK-model-based dosing regimens. To illustrate this, exposure of the aminoglycoside antibiotic amikacin in neonates gradually improved when a PK-model taking the current bodyweight, postnatal age,

and ibuprofen co-exposure into account, was implemented and prospectively validated.[20,21] Furthermore, additional dosing interval prolongations are needed for neonates with perinatal asphyxia treated with therapeutic hypothermia to avoid toxic trough levels.[22] This illustrates the relevance of assessing drug exposure in population-specific disease conditions.

Optimization of therapies with commonly used drugs can further benefit from preclinical studies. This was illustrated in two settings. First, juvenile animal PK models can be used to differentiate between the impact of perinatal asphyxia vs. therapeutic hypothermia on neonatal drug disposition, because this is not feasible in a clinical setting. The acquired knowledge can subsequently be integrated in PBPK models. Second, besides PK, also preclinical pharmacodynamic models are of add-on value to improve neonatal drug therapy. The glycopeptide vancomycin is used in neonates for suspected or actual cases of late onset sepsis in neonates, but optimal dosing is still lacking.[23] The current neonatal vancomycin pharmacodynamic target is derived from adults with methicillin-resistant staphylococcus aureus infections. However, coagulase-negative staphylococci are the most often isolated pathogens in late-onset sepsis in neonates.[24] Although continuous vancomycin administration could theoretically have benefits, such as improved AUC target attainment and fewer dose adaptations, a recent experimental preclinical model documented that continuous infusions may be associated with increased risk of emergence of antimicrobial resistance.[25]

Microdosing studies in children

Performing early-phase pediatric studies not aimed at therapeutic benefit may be challenging in children, as most jurisdictions only allow minimal risk and burden compared with daily activities. This is especially challenging for drugs with high safety risks or difficult PK profiles.[26] An interesting alternative for studies using "therapeutic" drug doses, are microdosing studies with either [^{14}C]labeled or unlabeled drugs. A microdose is defined as "< 1/100th of the no-observed-adverse-effect level or < 100 μg.[27] The [^{14}C]label allows quantification of extremely low plasma concentrations by accelerator mass spectrometry in only 10–15 μL plasma.[28]

The practical and ethical feasibility of pediatric [^{14}C]microdosing studies was previously shown.[26] For example, a Pop-PK microdosing study was designed with oral [^{14}C] paracetamol (acetaminophen) to study ontogeny of intestinal and hepatic paracetamol glucuronidation and sulfation in children 0–6 years of age.[29] This study design was easily accepted by parents, as reflected by the high informed consent rates. In addition, the developmental change of paracetamol metabolism from mainly sulfation in neonates to glucuronidation in older children was confirmed.[30]

Given that microdosing studies with [^{14}C]-labeled substrates are feasible and safe in children, as illustrated by the above, this is a valuable option to study pediatric PK of known compounds but also for new compounds during drug development. This approach is now recommended in the 2019 FDA (draft) Guidance: "General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products Guidance for Industry."[31]

DISCUSSION AND CONCLUSIONS

The updates given during the satellite meeting to the 10th Juvenile Toxicity Symposium are evidence of improved understanding on how to study PKs and predict dosing regimens in pediatrics. First, the increase in ontogeny data on drug metabolism and transport has improved confidence in ontogeny profiles. The integration of the isoform and organ-specific developmental patterns into PBPK models allows integration of age-related differences in PKs, for which examples were provided. Although PBPK is considered the gold standard for pediatric PK prediction, all necessary information is not always available. Depending on the age and mechanisms involved, simpler methods, such as allometry, allometry combined with maturation function, functions based on the elimination pathway, and linear models, were shown to perform well. Last, to overcome safety risks by studying the PK in very young children, microdosing could be a valuable tool to get a very early readout to age-related differences in exposure.

The use of *in silico* approaches, including PBPK modeling, in pediatric drug development is increasing; between 2008 and 2017, 15% of all the PBPK analyses included in the New Drug Application submissions to the FDA supported the evaluation of pediatric-related issues, such as initial dose recommendation for clinical trials.[32] This feat highlights the need for open science and model transparency in the area of model development. Collaboration is paramount for the expanded use of this approach; input from academia, clinicians, pharmaceutical industry, model developers, and regulators is necessary to further establish best practice. Good examples of recent initiatives to share knowledge and accelerate practices are the Pediatrics PBPK Working Group, the Innovation and Quality consortium, the European Paediatric Translational Research Infrastructure, Conect4children, and the Drug Disease Model Resource repository, in which model codes are published in an open science manner.

The pharmaceutical industry preferably starts pediatric drug development for older age groups, and it takes a long time before the very young patients are addressed. Clinicians would rather see faster targeting of the intended age groups, like neonates. In addition, based on regulatory experience gathered in the last 10 years,[33] the "age-staggered" medicine development approach, which implies starting by the older and going sequentially to the younger age groups, lead to delays in data availability. The result is prolonged off-label use in younger age groups (especially neonates) and difficulty in conducting any trial in these groups once the medicine is on the market.[34]

Despite our better understanding on pediatric PK and dose predictions, knowledge gaps remain for the closure of which recommendations were given. First, *in vivo* derived ontogeny profiles for some drug metabolizing enzymes appear to provide a more accurate PBPK prediction of pediatric drug disposition than ontogeny profiles

from *in vitro* studies.[11,12,35,36] The reasons for the difference in ontogeny patterns from *in vitro* and *in vivo* data are not clear. Discrepancies exist between published *in vivo* derived CYP3A4 ontogeny profiles.[11,12] Important factors in deriving these profiles include the effects of disease (e.g., enzyme suppression and altered drug-binding proteins), the relative specificity of the probe *in vivo* drug substrates to that enzyme and its extraction ratio,[37] which all require more research. Second, transporter ontogeny profiles are mainly based on mRNA and protein expression levels, but should be expanded to transporter activity data. Moreover, this meeting focused on PKs, but exposure-response is currently understudied and should also be considered. Preclinical pharmacology research can help to study specific disease-related aspects as a function of age, as well as its potential to affect the PKs of compounds. These aspects should be further explored, as preclinical-to-clinical translation of PKPD relationships is relatively complex and, in general, quantitative translation is poor. These efforts would allow use of these model approaches for personalized medicine, taking into account various covariates and thereby obtaining sufficient drug exposure in each patient.

In conclusion, the predictability of pediatric drug exposure may be improved by further exploring the impact of maturational and non-maturational covariates on pediatric drug disposition, improving available and developing disease-specific PK and PBPK models, prospectively validating model-derived dosing regimens, and application of microdosing methods, as well as sharing knowledge and data between industry and clinical practice. To further establish best practices for dose setting in pediatrics, more *in vitro* and *in vivo* research is needed on such aspects as age-related changes in the exposure-response relationship and also the impact of disease on PK. New information coupled with the refining of model-based drug development approaches will allow faster targeting of intended age groups and allow more efficient design of pediatric clinical trials.

Funding. No funding was received for this work.

Conflict of Interest. The authors declared no competing interests for this work.

1. Kearns, G.L., Abdel-Rahman, S.M., Alander, S.W., Blowey, D.L., Leeder, J.S. & Kauffman, R.E. Developmental pharmacology–drug disposition, action, and therapy in infants and children. *N. Engl. J. Med.* **349**, 1157–1167 (2003).
2. Badée, J., Qiu, N., Parrott, N., Collier, A.C., Schmidt, S. & Fowler, S. Optimization of experimental conditions of automated glucuronidation assays in human liver microsomes using a cocktail approach and ultra-high performance liquid chromatography-tandem mass spectrometry. *Drug Metab. Dispos.* **47**, 124–134 (2019).
3. Badee, J. *et al.* Characterization of the ontogeny of hepatic UDP-glucuronosyltransferase enzymes based on glucuronidation activity measured in human liver microsomes. *J. Clin. Pharmacol.* **59**(suppl. 1), S42–S55 (2019).
4. Mooij, M.G. *et .al* Ontogeny of human hepatic and intestinal transporter gene expression during childhood: age matters. *Drug Metab. Dispos.* **42**, 1268–1274 (2014).
5. van Groen, B.D. *et al.* Proteomics of human liver membrane transporters: a focus on fetuses and newborn infants. *Eur. J. Pharm. Sci.* **124**, 217–227 (2018).
6. Cheung, W.K. *et al.* A comprehensive analysis of ontogeny of renal drug transporters: mRNA analyses, quantitative proteomics and localization. *Clin. Pharmacol. Ther.* 106, 1083–1092 (2019).
7. Brouwer, K.L. *et al.* Human ontogeny of drug transporters: review and recommendations of the Pediatric Transporter Working Group. *Clin. Pharmacol. Ther.* **98**, 266–287 (2015).
8. De Schaepdrijver, L.M., Annaert, P.P.J. & Chen, C.L. Ontogeny of ADME processes during postnatal development in man and preclinical species: a comprehensive review. *Drug Metab. Dispos.* **47**, 295 (2019).
9. European Medicines Agency. Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation_en.pdf> (2018). Accessed October 3, 2019.
10. Shebley, M. *et al.* Physiologically based pharmacokinetic model qualification and reporting procedures for regulatory submissions: a consortium perspective. *Clin. Pharmacol. Ther.* **104**, 88–110 (2018).
11. Salem, F., Johnson, T.N., Abduljalil, K., Tucker, G.T. & Rostami-Hodjegan, A. A re-evaluation and validation of ontogeny functions for cytochrome P450 1A2 and 3A4 based on in vivo data. *Clin. Pharmacokinet.* **53**, 625–636 (2014).
12. Upreti, V.V. & Wahlstrom, J.L. Meta-analysis of hepatic cytochrome P450 ontogeny to underwrite the prediction of pediatric pharmacokinetics using physiologically based pharmacokinetic modeling. *J. Clin. Pharmacol.* **56**, 266–283 (2016).
13. Johnson, T.N., Zhou, D. & Bui, K.H. Development of physiologically based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents. *Biopharm. Drug Dispos.* **35**, 341–352 (2014).
14. Calvier, E.A. *et al.* Allometric scaling of clearance in paediatric patients: when does the magic of 0.75 fade? *Clin. Pharmacokinet.* **56**, 273–285 (2017).
15. Krekels, E.H.J., Calvier, E.A.M., van der Graaf, P.H. & Knibbe, C.A.J. Children are not small adults, but can we treat them as such? *CPT Pharmacometrics Syst. Pharmacol.* **8**, 34–38 (2019).
16. Calvier, E.A.M., Krekels, E.H.J., Johnson, T.N., Rostami-Hodjegan, A., Tibboel, D. & Knibbe, C.A.J. Scaling drug clearance from adults to the young children for drugs undergoing hepatic metabolism: a simulation study to search for the simplest scaling method. *AAPS J.* **21**, 38 (2019).
17. Calvier, E.A.M. *et al.* Drugs being eliminated via the same pathway will not always require similar pediatric dose adjustments. *CPT Pharmacometrics Syst. Pharmacol.* **7**, 175–185 (2018).
18. Allegaert, K., Mian, P. & van den Anker, J.N. Developmental pharmacokinetics in neonates: maturational changes and beyond. *Curr. Pharm. Des.* **23**, 5769–5778 (2017).
19. Allegaert, K., Simons, S.H.P., Tibboel, D., Krekels, E.H., Knibbe, C.A. & van den Anker, J.N. Non-maturational covariates for dynamic systems pharmacology models in neonates, infants, and children: filling the gaps beyond developmental pharmacology. *Eur. J. Pharm. Sci.* **109S**, S27–S31 (2017).
20. Smits, A., Kulo, A., van den Anker, J. & Allegaert, K. The amikacin research program: a stepwise approach to validate dosing regimens in neonates. *Expert Opin. Drug Metab. Toxicol.* **13**, 157–166 (2017).
21. Smits, A., De Cock, R.F., Allegaert, K., Vanhaesebrouck, S., Danhof, M. & Knibbe, C.A. Prospective evaluation of a model-based dosing regimen for Amikacin in preterm and term neonates in clinical practice. *Antimicrob. Agents Chemother.* **59**, 6344–6351 (2015).
22. Cristea, S. *et al.* Amikacin pharmacokinetics to optimize dosing in neonates with perinatal asphyxia treated with hypothermia. *Antimicrob. Agents Chemother.* **61**, e01282-17 (2017).
23. Vandendriessche, A., Allegaert, K., Cossey, V., Naulaers, G., Saegeman, V. & Smits, A. Prospective validation of neonatal vancomycin dosing regimens is urgently needed. *Curr. Ther. Res. Clin. Exp* **76**, 51–57 (2014).
24. Allegaert, K., Flint, R. & Smits, A. Pharmacokinetic modelling and Bayesian estimation-assisted decision tools to optimize vancomycin dosage in neonates: only one piece of the puzzle. *Expert Opin. Drug Metab. Toxicol.* **15**, 735–749 (2019).
25. Ramos-Martin, V. *et al.* Pharmacodynamics of vancomycin for CoNS infection: experimental basis for optimal use of vancomycin in neonates. *J. Antimicrob. Chemother.* **71**, 992–1002 (2016).
26. Turner, M.A. *et al.* Pediatric microdose and microtracer studies using 14C in Europe. *Clin. Pharmacol. Ther.* **98**, 234–237 (2015).
27. Food and Drug Administration US Department of Health and Human Services Guidance for Industry Investigators and Reviewers. Exploratory IND Studies. <https://www.fda.gov/media/72325/download> (2006).
28. Vuong, L.T., Blood, A.B., Vogel, J.S., Anderson, M.E. & Goldstein, B. Applications of accelerator MS in pediatric drug evaluation. *Bioanalysis* **4**, 1871–1882 (2012).
29. Mazaleuskaya, L.L., Sangkuhl, K., Thorn, C.F., FitzGerald, G.A., Altman, R.B. & Klein, T.E. PharmGKB summary: pathways of acetaminophen metabolism at the therapeutic versus toxic doses. *Pharmacogenet. Genomics* **25**, 416–426 (2015).
30. Mooij, M.G. *et al.* Successful use of [14C]paracetamol microdosing to elucidate developmental changes in drug metabolism. *Clin. Pharmacokinet.* **56**, 1185–1195 (2017).
31. US Food and Drug Administration. General clinical pharmacology considerations for neonatal studies for drugs and biological products guidance for industry (Draft). Accessed April 21, 2020.

32. Grimstein, M. *et al.* Physiologically based pharmacokinetic modeling in regulatory science: an update from the U.S. Food and Drug Administration's Office of Clinical Pharmacology. *J. Pharm. Sci.* **108**, 21–25 (2019).
33. European Medicines Agency. 10-year Report to the European Commission - general report on the experience acquired as a result of the application of the Paediatric Regulation. <https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/paediatrics_10_years_ema_technical_report.pdf>.
34. Ethical considerations for clinical trials on medicinal products conducted with minors. <https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_09_18_ethical_consid_ct_with_minors.pdf>.
35. Johnson, T.N., Rostami-Hodjegan, A. & Tucker, G.T. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin. Pharmacokinet.* **45**, 931–956 (2006).
36. Edginton, A.N., Schmitt, W., Voith, B. & Willmann, S. A mechanistic approach for the scaling of clearance in children. *Clin. Pharmacokinet.* **45**, 683–704 (2006).
37. Salem, F., Abduljalil, K., Kamiyama, Y. & Rostami-Hodjegan, A. Considering age variation when coining drugs as high versus low hepatic extraction ratio. *Drug Metab. Dispos.* **44**, 1099–1102 (2016).