

PERSPECTIVE

A best practice framework for applying physiologically-based pharmacokinetic modeling to pediatric drug development

Pediatric physiologically-based pharmacokinetic (PBPK) models have broad application in the drug development process and are being used not only to project doses for clinical trials but increasingly to replace clinical studies. However, the approach has yet to become fully integrated in regulatory submissions. Emerging data support an expanded integration of the PBPK model informed approach in regulatory guidance on pediatrics. Best practice standards are presented for further development through interaction among regulators, industry, and model providers.

INTRODUCTION

Physiologically-based pharmacokinetic (PBPK) models make optimal use of available data by marrying the complex interplay of physiological parameters with drug characteristics, thus representing a mechanistic approach to predict the pharmacokinetics (PKs) of drugs in different populations. Pediatric PBPK models account for the development of organs, including the ontogeny of specific enzymes and transporters involved in the absorption, distribution, metabolism, and excretion (ADME) of a specific drug. Although knowledge gaps remain, ongoing research relating to ADME processes in children has allowed refinement of relevant physiological parameters and integration of more complex models. Thus, PBPK models, which are increasingly used in pediatric clinical pharmacology, including drug development, are reaching maturation for applications with high regulatory impact.¹ This paper sets out some best practice standards with emphasis on small molecules for debate and further expansion.

INDUSTRY AND REGULATORY VIEW OF PBPK IN PEDIATRIC DRUG DEVELOPMENT

Legislation in both the United States (Pediatric Research Equity and Best Pharmaceuticals for Children Acts) and the European Union (Pediatric Regulation) mandate pediatric drug development by offering 6 months patent extension in return for conducting pediatric studies. These are defined in a pediatric study or investigation plan and have to be submitted to regulators early in drug development. Development plans are aimed at ensuring that necessary data are obtained through studies in children, to support the authorization of a medicine for children. Due to practical and ethical challenges in pediatric drug development, it is recognized that extrapolation approaches can be used to leverage all available information on the drug, the disease itself, and the expected outcome, in an attempt to minimize the impact on vulnerable pediatric populations without compromising the utility of the data to make an informed decision. As the number of patients available for studies is often small, model-informed drug development approaches, including PBPK modeling, form a central part of almost any pediatric drug development program.

According to a recent review,² 15% of drug submissions to the US Food and Drug Administration (FDA) between 2008 and 2018 involving PBPK modeling included simulations in pediatrics.² In addition to the typical applications outlined below, the FDA document cites a number of possible uses of PBPK in pediatric drug development; informing enzyme ontogeny using a benchmark drug and facilitating covariate analysis for the effects of organ dysfunction in pediatric patients. A report from an FDA public workshop suggests that allometry is reasonable for extrapolation of PKs down to 2 years with application of ontogeny and maturation via PBPK below

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this age. However, a recent paper³ argues against this 2-year cut off generalization between the two approaches, outlining the benefits of using PBPK modeling to address dose extrapolation or the drug-drug interaction (DDI) liability of drugs with complex ADME or formulation issues. The PBPK approach offers a canonical and integrative platform to:

1. Aid “first in pediatric” clinical trials by projecting starting doses (most common application) and optimizing study design.
2. Support the development of complex pediatric formulations and evaluation of the effects of co-administered foods (e.g., apple sauce) on PKs.
3. Support situations where recruitment of young patients and obtaining PK data is challenging, by supplementing limited observed clinical PK data with population simulations.
4. Simulate “difficult to test” scenarios in pediatrics such as DDI potential or the effects of specific diseases.³

An increasing number of examples of the application of PBPK to replace or inform studies in the pediatric population are beginning to emerge.⁴ PBPK simulations are used globally in regulatory submissions. The FDA,⁵ the European Medicines Agency (EMA),⁶ and the Pharmaceuticals and Medical Devices Agency (PMDA)⁷ guidelines support the use of PBPK models to determine the optimal dose for

children. Recent EMA guidelines present a framework related to the intended use of PBPK separated into low, medium, and high impact regulatory applications, which is linked to the required level of qualification, as summarized in Figure 1. However, a paper from a pharmaceutical industry consortium in response to both the FDA and the EMA draft guidelines regarding qualification and verification of PBPK models for regulatory submissions suggests more clarity and flexibility is needed.⁴ Best practice standards based on the intended use of the PBPK model, with particular emphasis on pediatrics, are clearly needed.

A BEST PRACTICE FRAMEWORK AND CASE STUDIES

The “learn and confirm” approach through data integration, continuous model refinement, and verification is recommended for PBPK modeling; final pediatric models may be the end result of a number of these cycles. Some best practice criteria relevant to steps within the approach or modeling ADME components of the drug are set out in Table 1. As a general rule, when possible, models are developed and verified (in terms of ADME mechanisms) in adults prior to moving to pediatric groups, typically consisting of adolescents, children, infants, and neonates. In rare cases, where adult data are not available, PBPK modeling will be initiated in the oldest age

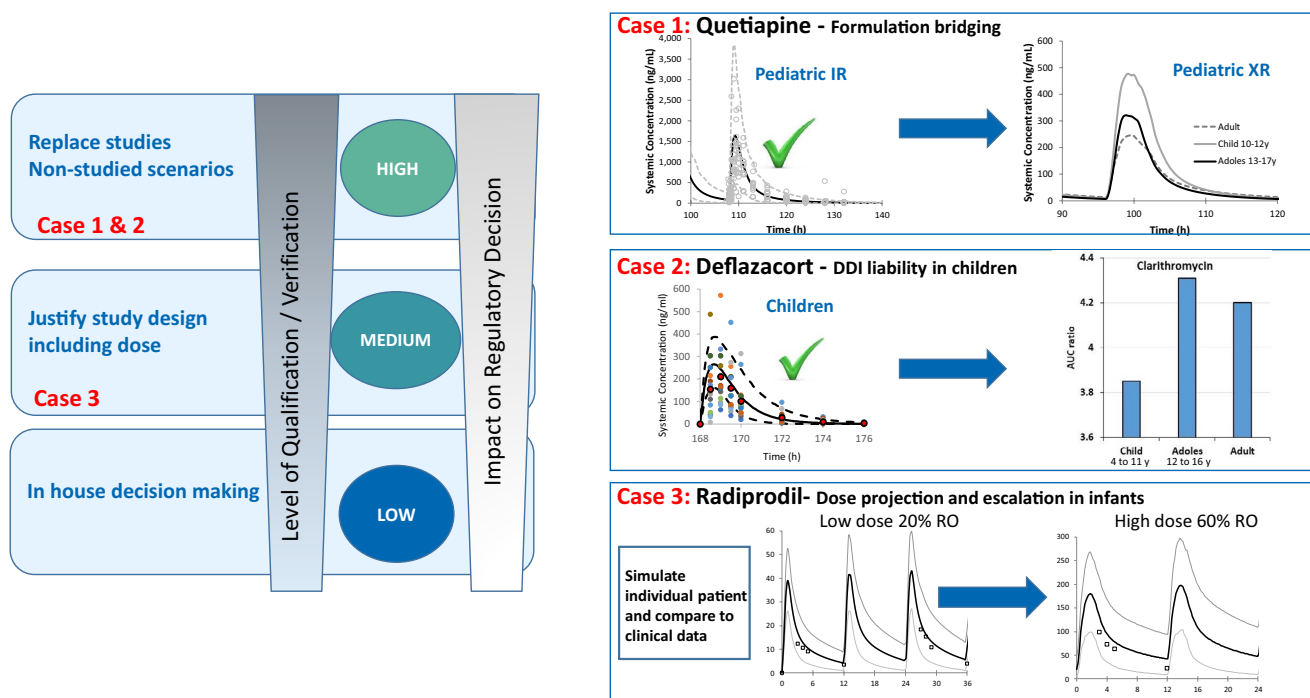


FIGURE 1 Framework for the use of virtual pediatric trials to support, complement or replace clinical studies based on regulatory decision impact and how the presented cases fit into this framework. DDI, drug-drug interaction; IR, immediate release; XR, extended release; RO, receptor occupancy

TABLE 1 Best practice framework for the use of pediatric PBPK modeling in drug development

| Best practice | Source of information | Case cross reference |
|---|---|--|
| General principles | | |
| Use a “learn and confirm” approach | In vitro and in vivo data. | Cases 1, 2, and 3 |
| It should be demonstrated that the PBPK drug model works well in a range of adult scenarios | Verification data from clinical studies: Single dose Multiple dose DDI | Cases 1, 2, and 3 |
| If necessary, start using PBPK model with older pediatric age groups first, verify, and move to younger groups | Clinical data. | Case 2 |
| For any uncertain parameters within the pediatric PBPK model perform sensitivity analysis if they are likely to have a significant impact | Global and/or local sensitivity analysis within PBPK platform | |
| For pediatric dose extrapolation using PBPK, as a safety net, compare with allometric scaling | | Case 3 |
| For patients with specific disease, determine whether there is any evidence indicating a disease effect on any system parameters | Literature data | Case 1 (schizophrenia lower CL vs healthy volunteer) Case 2 |
| Where PD is known, link this to PBPK if possible, especially important if PK/PD changes with age | Literature, experimental data | Case 3 |
| Predicting elimination | | |
| Knowledge of the fractional contribution of enzymes and transporters to major drug elimination pathways | Mass balance In vitro metabolism data Adult clinical PK and DDI data | Cases 1, 2, and 3 |
| Ontogeny is known for enzymes and transporters affecting ADME | Literature data, verification for drugs where PK influenced by same pathways. If ontogeny not known perform in vitro assessment | Cases 1 and 2, case 3 in vitro assessment |
| Renal elimination – evidence of active tubular secretion/ reabsorption. Ontogeny renal transporters | Is $GFR \cdot f_u \leq CL_R$. Literature data. | |
| For pediatric drugs eliminated by two or more pathways consider age related changes in DDI | Differential ontogeny of each pathway | Case 2 (but predominantly one pathway) |
| Predicting absorption | | |
| Any absorption issues are understood and can be simulated in adults. Assess if a mechanistic pediatric absorption model is needed for drug. | BCS class 2, 3, 4 – Permeability, solubility (FaSSiF, FeSSiF), transporters. | Cases 1 and 3 |
| Consider any information on specific pediatric drug formulations | Bioequivalence in adults, additional factors known to influence absorption, salts, co-solvents, different foods, etc. | Case 1 |
| Consider differences in pediatric food effect due to meal size, composition, and frequency. | Literature data | Case 3 |
| For poorly soluble drugs are there any likely consequences from reduced fluid administration and intestinal fluid volume in children? | BCS class 2 and 4 | Case 3 |
| Model verification (in relation to intended model use) | | |
| Systems parameters: sources of all system parameters are known and referenced | Population summary | Case 1, 2, and 3 |
| Verification data for drug model in adults | Clinical data | |
| Verification data on the same or similar drugs in pediatric population | Available clinical data | |

(Continues)

TABLE 1 (Continued)

| Best practice | Source of information | Case cross reference |
|--|---|----------------------|
| Systems parameters: verification data should match the age range of interest | Clinical data | Case 1 and 2 |
| Perform sensitivity analysis for any uncertain parameters to achieve greater clarity | Global and local sensitivity analysis tools | |

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; BCS, Biopharmaceutics Classification System; CL, clearance; CL_R, renal clearance; DDI, drug-drug interaction; FaSSIF, fasted state simulated intestinal fluid; FeSSIF, fed state simulated intestinal fluid; GFR, glomerular filtration rate; PBPK, physiologically-based pharmacokinetic; PD, pharmacodynamic; PK, pharmacokinetic.

group after careful consideration of known ontogeny. To reiterate, best practice has to be viewed in terms of the intended use of the model; when it is going to replace clinical studies, a higher level of verification, and confidence in the software for the intended purpose is required. Application of these standards is illustrated below using case studies linked to best practice criteria (Table 1) and the regulatory framework (Figure 1).

Case 1

Quetiapine is an atypical antipsychotic drug with high permeability and moderate solubility and defined as a Biopharmaceutics Classification System class II compound. A fully mechanistic pediatric absorption model within a PBPK modeling framework was applied to extrapolate an adult quetiapine extended release (XR) formulation dose to children (10–12 years) and adolescents (>12 to 18 years).⁸

- The model was developed in a healthy adult population using *in vitro* metabolism and clinical DDI data to calculate the fraction metabolized for CYP3A4, CYP2C9, and CYP2D6. Thereafter, the model was able to recapture the DDI among quetiapine and ketoconazole and carbamazepine in healthy adults.
- This was followed by model verification against observed data for the instant release (IR) formulation in both adult and pediatric patients.
- For the XR formulation, the release profile and colonic absorption was included in the model and verified against adult observed data.
- Finally, the model was used to bridge the formulations between adults and pediatric patients and to determine the appropriate pediatric dose.

Outcome

Predictions indicated that children and adolescents are likely to achieve a similar exposure following administration of either the XR or the IR formulation at similar total daily doses. This example was accepted by the regulators in lieu of further clinical studies.⁴

Case 2

Deflazacort is a glucocorticoid used to treat Duchenne muscular dystrophy (DMD). The target patient population is male children aged 5–15 years. The proposed dosing regimen for the drug is 0.9 mg/kg/day. Deflazacort is a pro-drug that is

metabolized rapidly in plasma by esterases to the active moiety 21-desacetyl deflazacort (21-desDFZ). The 21-desDFZ is mainly eliminated through CYP3A4-mediated metabolism. Children with DMD are likely to receive multiple drugs for treatment of their condition. Thus, PBPK modeling was applied to determine the DDI potential of deflazacort in children.

- A PBPK model was developed using observed PK data obtained following single-dose administration in healthy male adults.⁹
- The CYP3A4 component of the drug model was verified against clinical DDI data in adults with CYP3A4 perpetrators (clarithromycin and rifampicin).
- The model was further verified in children aged 4–11 years and in adolescents aged 12–18 years and was able to capture the concentration-time profiles (0.8 or 0.9 mg/kg daily) and PK variability. The 4–11 years group can be divided into smaller age ranges relevant to the disease profile and PK variability.
- The verified drug model was applied prospectively to simulate the effect of other CYP3A4 modulators on the PK of 21-desDFZ in children and adolescents.
- Predicted area under the curve (AUC) ratios of 21-desDFZ following co-administration of CYP3A4 inhibitors (clarithromycin and fluconazole) and inducers (rifampicin and efavirenz) were not significantly different among adults, adolescents, and children.
- If simulations of 21-desDFZ in children less than 2 years were performed, supporting documentation for predictions of the DDI potential of other similar CYP3A4 substrates may be required to demonstrate that the effects of CYP3A4 ontogeny could be captured.

Outcome

The PBPK predictions for the DDI in children and adolescents were accepted as supportive evidence for the proposed dosing recommendations on the deflazacort label.

Case 3

Radiprodil has potential in the treatment of rare infantile spasms. A PBPK model was developed and verified in adults,¹⁰ including a mechanistic absorption model to account for low solubility, the impact of fasted and fed luminal bile concentrations, and different formulations.

- The suspension formulation and relative amount of fluid administered with dose in the fasted state and effects on fraction absorbed was considered for the 2 to 14 month population.
- Radiprodil is metabolized predominantly in the liver by hydrolysis followed by decarboxylation and sulphation pathways where the ontogeny is unknown. In vitro incubation studies using hepatocytes prepared from neonatal, infant, child, and adult donors suggested no developmental pattern.
- Despite no specified ontogeny, PBPK modeling projected lower doses compared to the simpler three-fourth power allometric scaling approach.³
- To add an additional safety margin, the PBPK model was linked to a pharmacodynamic (PD) component via the theoretical receptor occupancy (RO), which in turn was linked to unbound concentration. The free drug brain to plasma ratio was one in preclinical species and selected target RO were 20%, 40%, and 60%.
- The doses projected to result in these RO were 0.04, 0.1, and 0.21 mg/kg; the initial dose gave a fourfold lower exposure compared to the typical 30 mg adult dose.

Outcome

Observed and predicted concentration-time data in the three infants recruited into the study were in close agreement. Despite the small number of subjects, this study demonstrates how detailed information can be compiled through a PBPK-PD modeling approach to guide a clinical trial in an orphan disease.

GOING FORWARD

High quality PBPK models based on qualitative and quantitative understanding of in vivo human absorption and clearance routes and their associated ontogenies can provide accurate predictions of PK and dose in a pediatric population. Encouraging publications on the performance of PBPK models, including comparisons of initial dose projections and actual clinical dose, will provide additional support leading to a more conclusive verification database. Verified models can be applied to “difficult to study” scenarios in the pediatric population, such as DDI prediction and ultimately for regulatory decision making. PBPK modeling is likely to play a larger role in pediatric drug development, including large molecules, which should be reflected by best practice standards endorsed by industry and regulators; this paper aims to set these out for further discussion and expansion.

DISCLAIMER




As an Associate Editor of *CPT: Pharmacometrics & Systems Pharmacology*, Karen Rowland Yeo was not involved in the review or decision process for this paper.

CONFLICT OF INTEREST

T.N.J., B.G.S., and K.R.Y. are employees of Certara UK Limited (Simcyp Division). E.G.B. is an employee of Certara NL (Integrated Drug Development). All authors declared no competing interests for this work.

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REFERENCES

1. Vercheijden LFM, Koenderink JB, Johnson TN, de Wildt SN, Russel FGM. Physiologically based pharmacokinetic models for children: starting to reach maturation. *Pharmacol Ther.* 2020;211:107541.
2. Grimstein M, Yang Y, Zhang X, 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.* 2019;108:21-25.
3. Ke AB, Johnson TN. Physiologically based pharmacokinetic modeling and allometric scaling in pediatric drug development: Where do we draw the line? *J Clin Pharmacol.* 2021;61 (Suppl 1):S83-S93.
4. Shebley M, Sandhu P, Riedmaier AE et al. Physiologically based pharmacokinetic model qualification and reporting procedures for regulatory submissions: a consortium perspective. *Clin Pharmacol Ther.* 2018;104:88-110.
5. General clinical pharmacology considerations for pediatric studies for drugs and biological products. Draft Guidance for industry. FDA (CDER), 2014. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-and-biological-products>. Accessed April 13, 2021.
6. Guidelines on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. EMA, 2016. Available from: https://www.ema.europa.eu/en/documents/scientific-guide-line/guideline-reporting-physiologically-based-pharmacokinetic-pbpbk-modelling-simulation_en.pdf. Accessed April 13, 2021.

7. Pharmaceuticals and Medical Devices Agency. Guidelines for Analysis Reports Involving Physiologically based Pharmacokinetic Models@ MHLW 2020. Available from: <https://www.pmda.go.jp/files/000239317.pdf>
8. Johnson TN, Zhou D, Bui KH. 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*. 2014;35:341-352.
9. FDA deflazacort clinical pharmacology review. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208684s000,208685s0001b1.pdf. Accessed April 13, 2021.
10. Johnson TN, Abduljalil K, Nicolas JM, et al. Use of a physiologically based pharmacokinetic– pharmacodynamic model for initial

dose prediction and escalation during a paediatric clinical trial. *Br J Clin Pharmacol*. 2020;87:1378-1389.

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