Physiologically-Based Pharmacokinetic Modeling for Drug Dosing in Pediatric Patients: A Tutorial for a Pragmatic Approach in Clinical Care

Joyce E. M. van der Heijden[1,*], Jolien J. M. Freriksen[1], Marika A. de Hoop-Sommen[1], Rick Greupink[1] and Saskia N. de Wildt[1,2]

It is well-accepted that off-label drug dosing recommendations for pediatric patients should be based on the best available evidence. However, the available traditional evidence is often low. To bridge this gap, physiologically-based pharmacokinetic (PBPK) modeling is a scientifically well-founded tool that can be used to enable model-informed dosing (MID) recommendations in children in clinical practice. In this tutorial, we provide a pragmatic, PBPK-based pediatric modeling workflow. For this approach to be successfully implemented in pediatric clinical practice, a thorough understanding of the model assumptions and limitations is required. More importantly, careful evaluation of an MID approach within the context of overall benefits and the potential risks is crucial. The tutorial is aimed to help modelers, researchers, and clinicians, to effectively use PBPK simulations to support pediatric drug dosing.

Study highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ A pragmatic physiologically-based pharmacokinetic (PBPK) modeling approach to predict pediatric pharmacokinetics has been shown to be feasible, although a thorough understanding of the model assumptions and limitations is required before model-informed doses can be recommended for clinical use.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ To describe the workflow for the best practice pragmatic PBPK modeling approach in pediatrics to eventually establish credible pediatric PBPK-based model-informed dosing (MID) recommendations.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This tutorial addresses important considerations in the best practice of re-using existing physiology and compound models to explore pediatric pharmacokinetic predictions, that is, a pragmatic PBPK modeling approach.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Pediatric MID recommendations can be implemented in clinical care to support or improve current dosing recommendations that are now only based on low levels of evidence.

Lack of clinical safety and efficacy data still leads to off-label drug prescribing in pediatric clinical care, despite the introduction of legislative initiatives (i.e., Best Pharmaceuticals for Children Act (BPCA), Pediatric Research Equity Act (PREA), and the EU Pediatric Regulation).[1] When age-appropriate dose recommendations are lacking, extrapolating pharmacokinetic (PK) data with physiologically-based PK (PBPK) modeling may be a solution to fill this information gap. PBPK modeling can reduce or replace clinical PK studies, for example, in the context of the pediatric study decision tree proposed by the US Food and Drug Administration (FDA).[2]

Physiologically-based pharmacokinetic modeling is a mechanistic approach to predict PKs in children based on drug-specific information accumulated in adult populations and physiology information of children of specific age groups. PBPK models consist of two distinguishable sets of data: physiology data and compound data. In theory, both compound and population models can be developed independently and can be linked, thereby re-using existing compound and population models. Hence, combining compound models with different population models would allow us to predict PKs of any drug in any population of interest, without the need to develop either for each new application.

Today, PBPK models are routinely applied in drug discovery and development, including first-in-human dose selection, management of clinical drug–drug interactions, and characterization of a food effect on drug dissolution and absorption.[3] The approach has been increasingly used to support pediatric dosing for recently

[1]Division of Pharmacology and Toxicology, Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands; [2]Department of Pediatric and Neonatal Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands. *Correspondence: Joyce E. M. van der Heijden (joyce.vanderheijden@raboudumc.nl)

Received June 12, 2023; accepted August 2, 2023. doi:10.1002/cpt.3023

approved drugs.[4] As such, pediatric PBPK (p-PBPK) simulations can go beyond the drug development process by informing off-label use in pediatric clinical care. For example, PBPK simulation results can help establish dosing recommendations or help increase the level of confidence of existing recommendations for medicines used to treat pediatric diseases.

Pediatric PBPK modeling studies have been published with the aim to establish model-informed dosing (MID) recommendations. Some studies only provide dosing recommendations for the age ranges for which clinical PK data were available, whereas frequently omitting the youngest age groups (e.g., (pre)term neonates and/or infants up to 2 years).[5–8] Others extended their dosing recommendations to younger age groups for which PK data are lacking.[9–11] In both cases, the models must be sufficiently robust and mechanistically well-parameterized to make informative prospective predictions of PKs in these younger pediatric age groups.

Building a compound model for p-PBPK modeling purposes from scratch can be time-consuming. However, for a large body of compounds, model information or model files are available in the public domain, for example, in peer reviewed journals, regulatory review documents, and model repositories of PBPK software developers. Often, these models were developed to simulate PKs in adult populations, and were rarely explored for their potential to guide drug dosing in children. A less time-consuming PBPK modeling approach in which pre-existing compound models are combined with pediatric physiology models can be pragmatic and feasible to predict PK and guide drug dosing in pediatric clinical care.[12,13]

Rapid growth of PBPK to support drug development decisions in the last decade resulted in active engagement of major regulators to develop guidelines around the use of this technology. The process is a work in progress. Currently available PBPK modeling guidelines from the European Medicines Agency (EMA) and FDA focus on the qualification of PBPK platforms and on the reporting of PBPK modeling studies.[14,15] Although describing the general process of model verification and application in scenarios where clinical data are available for model verification, these guidelines lack details on the modeling process itself and on important considerations that should be taken into account while conducting simulations. For example, how to conduct model verification when different sets of clinical data exist (e.g., data from diverse populations with differing underlying diseases) or when clinical data are sparse, is not further elaborated on in these guidelines. Besides regulatory guidelines, "best practice" papers for p-PBPK modeling have been published, including a tutorial providing a detailed description of full p-PBPK model development workflow.[16] These best practice papers generally focus on adult and pediatric model development from scratch. Because compound models as well as physiology models may already be available in literature or in databases, we here describe a "best practice" workflow when using p-PBPK to inform pediatric dosing in clinical practice in a pragmatic way, that is, taking these available models as a starting point.

THE PRAGMATIC PBPK MODELING APPROACH

A structured outline of a pragmatic PBPK modeling approach is provided, which addresses important considerations when re-using existing compound models to predict pediatric PKs (**Figure 1**). The framework includes four steps: (1) background information, (2) model requirements, (3) model verification, and (4) model application. In the first step ("background information"), the modeling objective, drug characteristics (such as the indications for use and the consequences of suboptimal dosing), and available PBPK models of the drug of interest are discussed. Next, the step "model requirements" includes a description of the modeling platform, as well as the physiology data and drug-dependent data. The step "model verification" follows and describes the search for clinical PK data required for assessment of model performance according to a defined model verification workflow. Last, the step "model application" details uses of the simulation results to support pediatric dosing recommendations, considering the assumptions regarding the model input parameters which may lead to uncertainties in the modeling results.

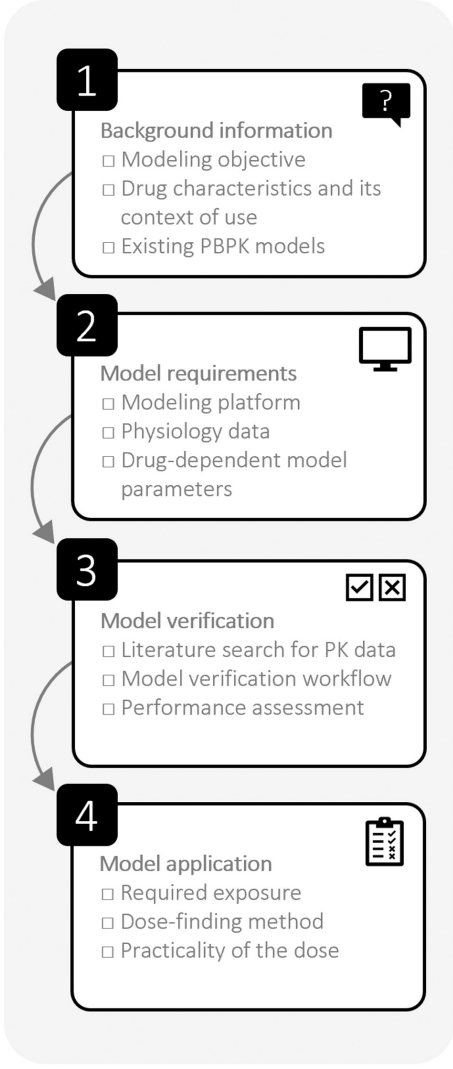

Figure 1 Pragmatic PBPK modeling workflow. Visualized workflow addressing the four main steps and their subtopics when applying the pragmatic PBPK modeling approach. PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic.

BACKGROUND INFORMATION

Modeling objective

A specific clinical or scientific question and a corresponding specific modeling objective, often dictates a p-PBPK modeling study. It is therefore imperative that clinicians are involved in the discussion how to approach the problem, already in the early stages of the modeling process. Requirements and decisions that need to be made during PBPK modeling are case-dependent. The level of mechanistic model parameterization, the need to include additional verification steps, and sensitivity analyses rely on the modeling objective. In the context of off-label dosing in clinical care, objectives for p-PBPK modeling can be: (1) to support or refine a current dosing recommendation that is associated with a low level of evidence from clinical studies,[17] (2) to establish a dose recommendation for a new indication and disease population or a new age group (drug is already prescribed to pediatric patients for another indication and disease population or another age group), and (3) to establish a new pediatric dose recommendation (not yet prescribed to pediatric patients).

Drug characteristics and its context of use

Information regarding physicochemical and PK properties, as well as the context of its clinical use are crucial to conduct PBPK simulations properly and to facilitate implementation of PBPK modeling results in clinical practice.

Intended indication(s). All indication(s) for which the drug is used in the clinical setting should be summarized (both registered and off-label). It is helpful because if there are no PK data available for the indication of interest, PK data from another indication may be used for model verification (see step Literature search for PK data).

Current clinical dosing guidelines. Current dosing recommendations in pediatrics can be found in, for example, the Summary of Product Characteristics, national/regional pediatric formularies (if available), or handbooks such as Lexicomp and IBM Micromedex. For certain drug classes, specific dosing guidelines are available, such as the World Health Organization (WHO) pediatric dosing dashboard for antiretroviral drugs.[18] Evidence used to support dosing recommendations can differ substantially between sources, potentially resulting in different dose recommendations among the guidelines. One can evaluate the evidence base and line of reasoning behind dosing recommendations to assess the strength and usefulness.

Available formulations and route(s) of administration. Describe the available formulations and, relevant route(s) of administration of the drug of interest, both for adults and for pediatric patients, and pinpoint the relevant route of administration in view of your modeling objective. Note that age-specific formulations may be available for the drug of interest, such as suspensions, chewable tablets, or fast dissolving tablets.

Route(s) of elimination. Relevant elimination pathways and their relative contribution to total elimination should be known in order to evaluate whether the PBPK model is adequately parameterized for the population of interest. Hence, ideally, a mass balance diagram of the drug disposition with the fractions metabolized by specific enzymes and/or fraction eliminated by the kidneys is available,[19] preferably per age group. A word of caution is needed, as elimination pathways and their relative contribution to clearance (CL) may change throughout the pediatric age span, examples are acetaminophen[20] and caffeine,[21] and hence extrapolation from adults to children should take this into account.

Plasma exposure target/therapeutic window. Knowledge of the drug- and population-specific (if available) therapeutic window or a more specific plasma exposure target is essential for establishing an MID. An example of a measure which relates plasma exposure to pharmacodynamics (PDs) is the "% time above the minimum inhibitory concentration (MIC)" which is used as surrogate therapy goal of several antibiotics.[22] To relate PK exposures to an effective dose, these conditions are essential. In this step, the information gap regarding the drug's therapeutic window or a specific PD-related plasma target level should be reported. In that case, the MID can often be established assuming exposure matching (step 4). When no exposure can be related to an effective dose (i.e., when no exposure matching is possible), one may consider other approaches to support dosing recommendations, such as PD models which do not require any drug concentrations (i.e., so called kinetic-PK models).[23]

Risk of suboptimal exposure. For final model evaluation and application (steps 3 and 4), it is essential to recognize the potential risks and consequences of under- and overdosing of the drug. In addition, it should be evaluated whether these risks and consequences differ between age groups and this should be weighed against the level of certainty in an MID. In case of, for instance, a narrow therapeutic window and severe side effects, it is essential to have stronger confidence in the accuracy of the PBPK modeling output.

Existing PBPK models

Existing physiology and compound models can generally be obtained from three distinct sources. Both types of models can be readily available in dedicated modeling software, in a model repository, or published in peer reviewed literature. Many high-quality compound models, but also lower quality compound models, have been built and published, using both commercial and open source PBPK software platforms. Models readily available in the software, for example, as available in Simcyp (Certara UK Limited, Simcyp Division, Sheffield, UK) are considered as high quality for specific modeling purposes as these are most often used, verified, and updated if necessary. Nevertheless, in our pragmatic approach, we always assess whether the compound model is fit-for-purpose to predict PKs in the pediatric population, specifically. For example, the compound model might have been developed to serve as a so called "perpetrator drug model," enabling the simulation of potential drug–drug interactions (DDIs). This allows a rather simple mechanistic parameterization of the elimination processes (i.e., total body CL instead of enzyme-specific CL), which makes it unsuitable to predict PKs in pediatric subjects. Models from

a repository or from scientific literature (e.g., obtained upon request from the corresponding authors) may also still be easily uploaded in the software, although sufficient quality of the model is not always ensured for the same reason as described above. If no compound or physiology models are available, rebuilding a model based on reported input parameters provided in scientific literature is a third option, but this can be challenging as parameter values might be incomplete or reported in an ambiguous manner. Consequently, this might be time-consuming and may impede one's ability to properly copy parameters from published models. If no compound model is available for the intended modeling software, but for another software, it is important to note that compound data are not always directly interchangeable. For example, similar CL processes are available in software tools like Simcyp and PK-Sim, varying from specific intrinsic CL values for metabolizing enzymes to total organ or plasma CLs.[24,25] Yet, depending on the type of data used, for instance, experimental *in vitro* data, this is linked to the *in vitro-in vivo* extrapolation procedure that is used by the software, that is, it is a very specific aspect which should be handled with care.

MODEL REQUIREMENTS

Modeling platform

Many software tools are available to conduct PBPK modeling: general-purpose modeling tools, such as R, MATLAB, and Berkeley Madonna, but also dedicated user-friendly PBPK software platforms, such as GastroPlus (www.simulations-plus.com), PK-Sim (www.open-systems-pharmacology.org), and Simcyp (www.simcyp.com). The PBPK modeling platform should be qualified for the intended purpose and the extent of qualification required depends on the clinical impact of the modeling.[14,26] As the aim of the studies targeted in this paper is to conduct PBPK model simulations to establish MID for pediatric patients in clinical care, it is necessary to use a robust and well-qualified PBPK modeling software platform. This tutorial will further focus on the use of dedicated PBPK modeling platforms. To note, these software tools are updated regularly which can include new data or tools. A compound model developed with an earlier software version might not be reproducible in a later version due to these adjustments. Therefore, if simulations are performed with a later software version than the version in which the compound model was developed, one should verify if it is still performing well.

Physiology data

Dedicated PBPK modeling platforms provide a number of pre-parameterized physiology population models, such as a healthy volunteer, pediatric, pregnant, and a renally/hepatic impaired population. Most of these models are considered qualified, as they have often been tested and used by a large number of users.[27] This is an important feature enabling broad and routine use of PBPK by drug developers and regulators. Availability of a healthy adult physiology population model is always required, regardless of the modeling objective, because healthy adult model verification needs to be performed before continuing to pediatrics to avoid that compound models with poor predictive performance in adults would impact subsequent predictions in pediatric populations.[28]

Next, depending on the modeling objective, a pediatric and/or a (pre)term neonate population model is required. Pediatric physiology models incorporate age-related changes in, for example, organ blood flows, organ volumes, plasma protein concentrations, and drug metabolism capacity, and, increasingly, drug transporter expression. A recent review describes the current status of p-PBPK models and the developmental changes in physiological parameters.[27] Qualification of these physiology models should be fit-for-purpose for specific applications, meanwhile be continuous as new knowledge becomes available, and the effort is anticipated to be non-trivial. Therefore, dedicated platforms are advantageous for effective and efficient use of p-PBPK in clinical practice. Because our knowledge on pediatric physiology continues to evolve, one should always be cognitive to uncertainty regarding certain physiological parameters and present alternative solutions (e.g., through sensitivity analyses) to support decisions. One should also realize that characteristics of the virtual pediatric populations available in different PBPK software platforms may differ, which will have consequences for model output, for example, the impact of variation in parameterization of pediatric population models on PKs has been investigated for tramadol.[29] The authors show that minor physiological differences (e.g., fraction unbound in blood, liver weight, and enzyme abundance) between the virtual populations resulted in different predictions of tramadol CL, indicating the relevance of conducting sensitivity analyses in case of uncertainty with regard to physiological parameters.

To predict PKs in pediatrics accurately, it is essential that ontogeny profiles of relevant metabolizing enzymes, for example, cytochrome P450 (CYP) enzymes or uridine 5′-diphospho-glucurono syltransferases (UGT), and drug transporters, for example, organic anion transporters (OAT) or P-glycoprotein (P-gp), relevant for PKs of a drug of interest are incorporated adequately in the models. Ontogeny profiles of drug metabolizing enzymes and transporters have been outlined previously.[27,30] Ontogeny functions can be based on *in vitro* or *in vivo* data, or combinations thereof, and can differ depending on the approach used.[30] Upreti *et al.*[31] showed that PK predictions were more accurate when based on ontogeny functions derived from *in vivo* data compared with when *in vitro* data were used. It is important to assess if and how ontogeny of the relevant enzyme(s)/transporter(s) involved in the disposition of the drug of interest are incorporated in the model. Once again, for distinct enzymes or transporters, ontogeny profiles are already provided in several dedicated PBPK platforms, and users have flexibility to re-parameterize ontogeny profiles in situations when there is no consensus on a specific ontogeny profile, or when the user is aware of significant differences among specific platforms. As mentioned earlier, the current best practice is to perform simulations reflecting available options to reveal which one captures clinical PK better and hence considered most realistic.[32] Still, ontogeny profiles of many transporters are not yet defined, which results in a knowledge gap, for example, in predicting renal tubular secretion or tubular re-absorption in young children.

When PKs are simulated for renally cleared drugs, is it important that the renal function is defined in the pediatric and preterm populations. Although renal transporters can have substantial impact on PKs, in most models, renal function largely depends on the

glomerular filtration rate (GFR). The most commonly used marker to estimate GFR is serum creatinine and several equations have been developed for calculating GFR based on serum creatinine and patient characteristics (e.g., age, body height, and weight).[33–40] Equations used to define GFR maturation in pediatrics and (pre) term neonates differ between PBPK modeling platforms. If emerging data warrant an alteration of the GFR calculation in the modeling platforms, this can be done manually. For example, recently, an individual patient data meta-analysis provided data to support a new equation for serum creatinine-based GFR estimations for term neonates.[41]

Drug-dependent model parameters

For our pragmatic approach to be successful, fit-for-purpose compound models are needed. Recently, a tutorial has been published describing the best practice approach for compound model development in Simcyp.[24] It is important to assess model parameterization critically, especially when a compound model is obtained from a repository or literature. One needs to check if all input parameters, required to run a simulation, are mentioned in the published PBPK study. Although parameters are software-dependent, a general consideration is described below.

Each software platform requires physicochemical and blood binding properties. Examples of physicochemical parameters are molecular weight, lipophilicity, acid dissociation constant, blood-to-plasma partition ratio, fraction unbound, main plasma binding protein, and solubility of the compound. These parameters form the basis of the compound model and are ideally obtained from experiments,[24] although also *in silico* derived values can be used in the case of absence of experimental data. The latter is very common in early drug research and development, but it usually is not the case in view of the clinical application that this tutorial addresses, where measured data are usually available for parametrization.

If PKs are predicted upon oral administration, adequate incorporation of parameters describing its absorption is essential. Depending on the type of drug a simpler or more complex absorption model can be selected in most dedicated platforms. For example, first-order absorption model (empirical) and Advanced Dissolution Absorption Model (fully mechanistic) are available in Simcyp software. In terms of a pragmatic approach, particularly when drugs are only administered parenterally and also do not enter in enterohepatic circulation, empirical parameterization of oral absorption in available compound models may be adequate.

In terms of distribution, ideally, a multicompartmental modeling structure – with each organ and tissue represented separately – should be selected to reflect age-specific physiological changes on an organ level. But again, simpler distribution models can be acceptable for molecules exhibiting very small volumes of distribution, for example, for molecules remaining largely in the systemic circulation. The empirical parameterization of volume of distribution (V_d) is available in the major dedicated platforms. Methods to predict tissue partition coefficients are developed by, for example, Berezhkovskiy,[42] Rodgers and Rowland,[43] Poulin and Theil,[44] and Schmitt,[45] to allow the use of the so-called full-PBPK distribution model. The applied prediction method should be appropriate for the drug of interest. For clinical MID purposes, describing drug distribution using prediction methods alone may not be sufficient. In compound models, it is therefore very common to calibrate initial predictions to clinical data (i.e., a middle-out approach). When using existing compound models, one should be aware whether such an approach has been taken.

As for CL, accurate mechanistic parameterization of drug elimination is essential to accurately predict PKs in pediatrics. Ideally, all elimination pathways and their relative contribution for a drug molecule should have been quantitatively determined prior to the approval of the drug (also see Drug characteristics). In case metabolizing enzymes, for example, CYP and UGT enzymes, are involved, compound models generally include intrinsic CL values (assuming linearity of CL across concentrations) or Michaelis–Menten kinetics (capturing saturation or nonlinearity) to describe the rate of metabolism. One should confirm whether the parameters are specified per contributing enzyme, in order to connect with the ontogeny profile within the physiology model. The same applies to drug transporters. When taking a pragmatic modeling approach based on existing compound models, one should be aware that authors sometimes may have chosen to generalize a smaller or larger part of CL and not to attribute it to specific CL routes or mechanisms when not all relevant elimination pathways are identified and/or quantified. For their purpose, this may have been an acceptable assumption, but this is not necessarily the case for p-PBPK modeling that aims to establish clinical dosing. Note that nonspecific CL is often scaled allometrically or not at all, that is, assuming that there is no ontogeny in metabolizing enzymes, transporters, or changes in organ blood flow. This may lead to suboptimal model performance for MID.

In case a compound model is rebuilt based on published data, the sources of the input data should be assessed to examine the reliability (e.g., a trustworthy source is used), the accuracy (e.g., possible typing error) and the evidence (e.g., if it is an *in silico*, *in vitro*, *ex vivo*, or *in vivo* derived value). For example, PubChem[46] and DrugBank[47] are reliable web tools for physicochemical properties, whereas absorption, distribution, metabolism, and excretion (ADME) properties are often provided in published articles, such as intrinsic CL values for specific metabolizing enzymes, which ideally support each other's findings. Additionally, if published PK data were used for model building or refining, for example, when calibrating V_d as mentioned earlier, these studies should not be used for model verification (see below Model verification). It is valuable to compare the clinical study from which data were used for model parameterization, with those observed in other clinical studies. If the clinical data used, deviates from data reported in other studies, the parameter value that was derived from this specific study might not be generalizable and the cause should be documented (e.g., used parameter value is influenced by disease state). Preferably, parameter estimation methods should have been provided in a supplementary file to paper/compound model. In case input parameters are missing, these could be acquired either by contacting the author, via papers the authors refer to, or by conducting a literature search for other supporting data.

In summary, one should understand how a compound model was built and which *a priori* assumptions were made, before applying it for pediatric simulations. Although reviewing the parametrizations

requires some due diligence, it still is much less laborious compared with building compound models from scratch, particularly when considering the many well-defined and described models that are out there.

MODEL VERIFICATION

Before a PBPK model can be applied for prospective predictions of PKs and to guide dosing, the model needs to be verified to assess whether it is fit-for-purpose.[48] To describe the qualification of PBPK models, various terminology has been used, that is, verification vs. validation.[49] Here, verification describes the process of determining model performance, that is, the accuracy of the model to predict observed data. Similar to qualification of a physiology model, continuous updating of compound models that describe the drug-specific aspects to PBPK modeling, is an important feature for a mechanistic model like PBPK. For example, if new information becomes available, such as transporter abundance or enzyme ontogeny, ideally, physiology models are updated to reflect the latest state of knowledge. Thus, the model verification steps described below not only serve the purpose of determining the performance of the compound model selected in step 2, but also provides a learning opportunity to improve both compound and physiology models for effective applications (step 4).

Literature search for PK data

Clinical PK data are required to verify the model. Literature databases (such as PubMed and Embase) should be searched for adult and pediatric PK data. Two proposed search queries for PubMed are included in the **Supplementary Materials**. Preferably, multiple (≥ 3) PK studies should be included for model verification per age group and per route of administration (and single and multiple dose studies), if available. To note, studies which should be excluded for model verification are DDI studies where the drug of interest is administered concurrently with a perpetrator drug with which it interacts. In addition, the health status (e.g., underlying disease) of the studied population is preferably in accordance with the status of the population of interest to exclude an impact of disease on PK. If only PK data are available for other indications/diseased populations, one should note the underlying assumptions on the disease related PK difference (see paragraph Pediatric and preterm model verification, scenario 2).

Study design characteristics should be extracted, including the number of subjects, health status/underlying disease, age range (postnatal age with gestational age in case of neonates), proportion of women, co-medication, administered dose and route of administration (including intravenous infusion duration, dosing interval if administered more than once, and the prandial state in case of oral administration), and the study duration. Ensuring that the demographic characteristics of your virtual population match as closely as possible with the reported population will result in meaningful interpretation of simulated mean PK parameters as well as corresponding variability.[50] Although, in case large interindividual variability in PKs is observed *in vivo*, and PK studies are abundantly available, one can include more PK studies to appraise the extent of the variability in PK data. An example is propofol, where a large variability is seen in the estimation of CL and V_d in adults.[51] Of note, the extent of variability observed in children should not deviate from the extent observed in adults.

Model verification workflow

We described a pragmatic workflow for pediatric PBPK model verification before, applying it to several drugs.[13] In this approach, a PBPK model is first verified with an adult population to demonstrate adequate predictive performance when predicting PKs in adults before integrating age-related physiological changes to predict PK in pediatrics and subsequently, if relevant, in preterm neonates. Below we describe relevant steps in more detail and we outline how the approach can be applied in three scenarios of decreasing clinical data availability for model verification.

Conducting a virtual verification simulation. Required input information for the population and compound models is described in the section Physiology data and Drug-dependent model parameters. Next, a virtual study should be designed to conduct a simulation. Generally, simulations comprising 100 virtual subjects per simulation are considered useful to obtain a notion of model performance. Yet, in some cases, it might be necessary to simulate larger virtual populations, for instance, if the pediatric age range is very wide. To run a virtual trial resembling the clinical PK study, the study characteristics need to match as closely as possible. This includes the age range (including the gestational age when a preterm population is simulated) and the gender ratio of the population as well as the dose (as mg, mg/kg, or mg/m^2), route of administration, number of doses, dose interval (if applicable), prandial state, and study duration. With respect to the route of administration, the intravenous (i.v.) and oral (p.o.) routes can generally be selected in all PBPK modeling platforms.

Adult model verification. Model performance should first be evaluated upon i.v. administration before continuing to oral administration as i.v. simulations allow us to visualize distribution and CL processes in the model independent from drug absorption and first-pass metabolism.[52] Next, if PK data are available and if the scenario is clinically relevant, simulations upon both single and multiple administrations should be performed to evaluate the ability of the model to predict PKs upon multidose administration (e.g., steady-state) as well. Aside from the fact that many drugs are dosed up to steady-state, and one needs a way to verify model performance for predicting it, including multidose simulations, is especially important for drugs with auto-induction or auto-inhibition of metabolism, such as carbamazepine.[53] Such situations put more demands on the mechanistic parameterization of the compound model, which needs to be verified for multiple dosing scenarios. Additionally, PK studies should, together, cover a broad dosing range to ensure that the model can predict PK for both low as well as high dosing strategies (i.e., assess dose nonlinearity, e.g., to enzyme saturation). If a high number of PK studies are available, preferably all available data should be used, but studies with the highest number of study subjects and studies reporting both plasma concentration-time data and multiple PK parameters should be prioritized. If a complete sense of model

verification can be acquired with these PK studies, inclusion of more studies may not be necessary.

Pediatric and preterm model verification. Pediatric clinical PK data, especially for term and preterm neonates, are less abundant compared with adult data. Hence, model performance cannot always be evaluated for the specific pediatric age range and indication of interest. However, if high confidence in model performance is established for children of a different age range or for another indication, if the model is mechanistically adequately parameterized and PK can be assumed with confidence to be similar among indications (e.g., negligible effect of the disease of the new indication on drug absorption and disposition) then the model may still be regarded as "fit-for-purpose." At this point, the available p-PBPK model can be considered the best there is to make an educated estimation of expected exposure, in the face of absence of any clinical data. Particularly when the p-PBPK model was shown to simulate adequate exposures in that specific age group for another drug with comparable disposition characteristics (e.g., metabolic CL route, V_d, and protein binding). **Figure 2**, shows 3 scenarios of clinical data availability (i.e., PK data available, PK data available for a different age group or indication/disease state, and limited to no PK data available) with their corresponding assumptions and uncertainties that need to be considered.

Scenario 1: In case PK data are available for the age group and indication of interest, model verification should be conducted against the available clinical data. Note that the current pediatric population models used in dedicated PBPK modeling platforms generally represent healthy children, whereas PK data used for verification obtained in clinical studies are derived from diseased children. Hence, within this scenario we need to make assumptions to what extent disease state may affect PKs. The model verification workflow remains the same for any situation, that is, model verification will be performed against the available clinical data. But of course, the interpretation should be different. When no disease effect on PKs is assumed, one can simulate untested dosing scenarios and interpret the MID with high confidence. Yet, when one is aware that disease has an effect on PKs, and predictions are not in line with the observed, effects of the condition on PKs and the implications for dosing should be discussed critically (this applies to the following two scenarios as well). An example in which the disease state can substantially alter PKs of a drug is that the distribution of a drug may be increased in burn patients.[54] Moreover, potential treatments may also affect PKs, for example, therapeutically induced hypothermia,[55] or extracorporeal membrane oxygenation.[56]

Scenario 2: In case PK data are only available for a different age range and/or indication and disease state, model verification should be conducted with those available clinical data. Firstly, when PK data are available for another pediatric age group, PBPK model performance is verified for that age group. Using this model to subsequently predict PKs in other age groups requires a mechanistically well-parameterized compound model (i.e., well-defined drug elimination pathways) as this will increase the confidence in the PK predictions for the age group for which no PK data are available. Second, when PK data are available from a population with another indication and/or disease state, a thorough understanding of the potential effect of the disease state on PKs is required before untested dosing scenarios can be simulated.

Scenario 3: In case limited or no PK data are available, it is more difficult if not impossible to verify the model for the drug and population of interest. Again, assumptions in the first and second scenario apply here as well. Yet, here in the absence of data from the drug of interest, model performance can be verified using PKs from a comparable drug, that is a drug with similar ADME properties. For example, when the goal is to simulate PKs of a CYP3A4 substrate, that exhibits 90% binding to plasma albumin, has no renal CL and for which no clinical verification data are available, then a different drug with similar characteristics for which the clinical PK data are available needs to be simulated and verified against available clinical data of this drug. Including a minimum of two comparable drugs is suggested.[14] In the case of adequate performance, confidence in model performance for the drug of interest also increases as it is demonstrated that for drugs with a similar disposition pathway the model works. Because it may be difficult to select comparable drugs with a 100% match in disposition characteristics, it is crucial to document these small differences between drug characteristics in order to evaluate how this may affect confidence in model performance for the drug of interest. One example is, in cases where multiple CYPs contribute to CL, two comparable drugs may qualitatively make use of the same CYPs for CL, but they may exhibit a different quantitative contribution of these elimination pathways to overall CL. This is a likely scenario, as for most drugs, several elimination pathways contribute to total CL to different extents (e.g., renal CL, biliary CL, and/or metabolism via multiple enzymes).[57] Thus, a discussion on how relevant these differences are in terms of building confidence for PBPK predictions for the drug of interest needs to be part of the verification procedure. If the overall trust in model performance is insufficient, for example, when comparable drugs are not simulated accurately, the proposed pragmatic modeling approach cannot be applied before additional relevant clinical data are available.

Assessment of model performance

There is no general consensus yet on criteria to accept model performance. Many argue that the criteria should be set on a case-by-case basis, as it is dependent on the intended use, therapeutic area, and potential safety and efficacy issues.[58] Moreover, important to note is that in pediatrics the response to drugs may show (unidentified) age-related variation, potentially resulting in a different therapeutic window compared with adults.[59] Dependent on the therapeutic window in adults (wide or small) and the consequences of over- or underdosing, criteria for model-acceptance could be adjusted. This, however, is not yet generally applied.

Still, there are two major approaches that are currently often used to assess model performance, that is, by means of a visual predictive check (VPC) of the agreement of the observed vs. the predicted plasma concentration-time curve and by calculating predicted-to-observed PK parameter ratios. Multiple options have been described on how to quantitatively determine if a VPC and a PK parameter ratio are acceptable.

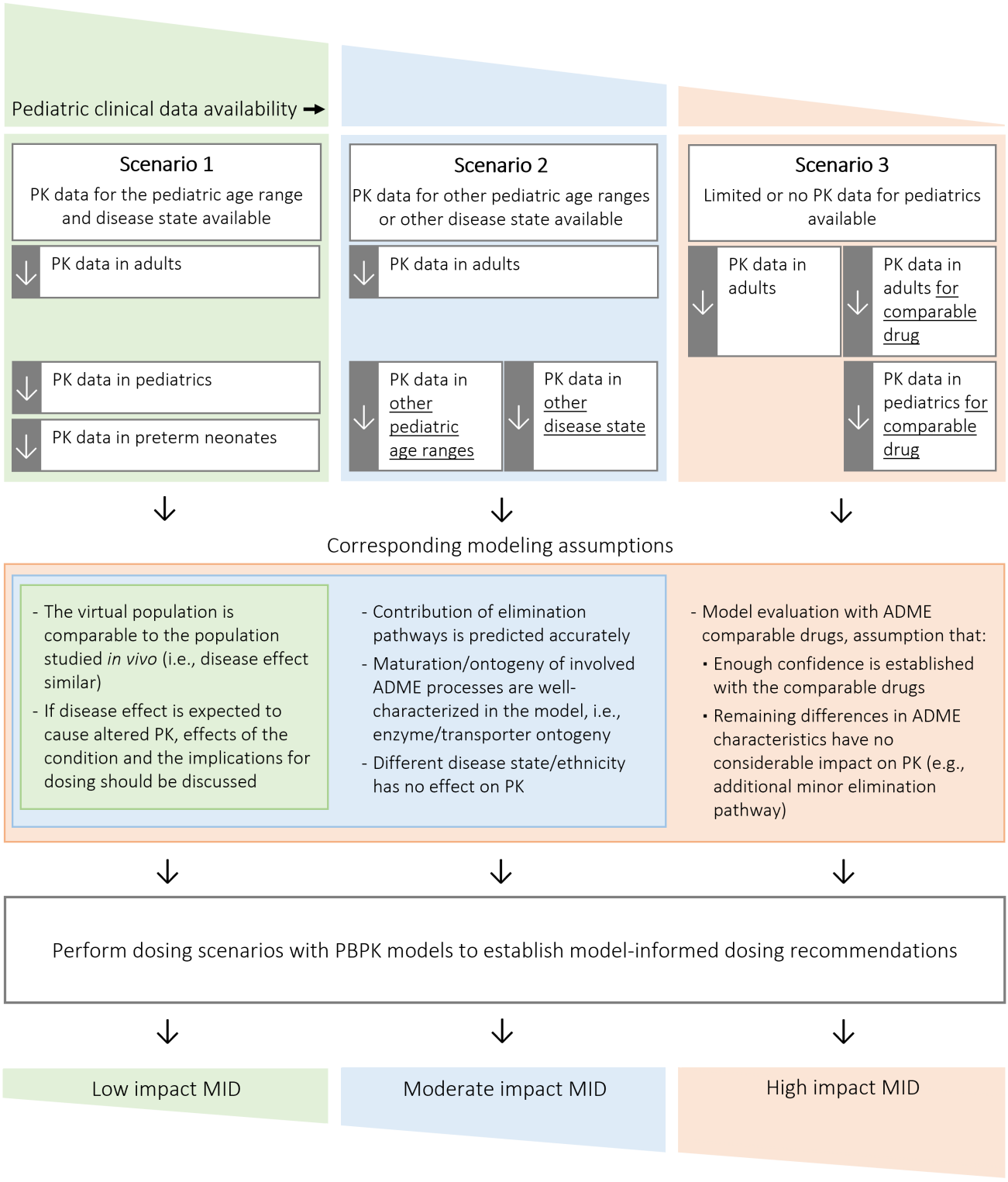

Figure 2 The PBPK model verification workflow, per clinical data availability scenario with their corresponding assumptions and uncertainties that need to be considered when applying the model to establish MID. In the lower part of the figure, the level of impact of modeling on clinical decision-making is indicated for the different scenarios. ADME, absorption, distribution, metabolism and excretion; MID, model-informed dose; PKs, pharmacokinetic(s).

Visual predictive check. The VPC is a qualitative measure to evaluate model performance, by comparing the shape of the predicted plasma concentration-time curve with the observed data. Both observed individual values as well as study means with corresponding interindividual variability are often used, given the dependency on how the clinical data for comparison

were reported. As common in other fields of PKs, both linear and semilogarithmic plots should be presented to visualize the different phases of drug disposition clearly. A linear plot is helpful to visualize maximum plasma concentration (C_{max}) and area under the curve (AUC), whereas a semilogarithmic plot is helpful to visualize the terminal half-life more clearly. In addition to qualitative assessment, it is highly recommended to some extent quantitatively to assess VPCs as well. One method is to calculate the percentage of observed individual plasma concentration measurements which fall within the predicted range of possible concentrations, yet this measure is most convenient when observed individual plasma concentration-time values are provided. Other measures which can be used to quantify the VPC are the prediction error (PE),[60] the average fold error (AFE), the root mean squared error (RMSE), the absolute average fold error (AAFE), or the more recently proposed normalized prediction distribution error.[61] It is optional to include both a measure for model bias (e.g., PE or AFE) and one for precision (e.g., RMSE or AAFE) to determine model accuracy. Again, no strict guidelines are available yet that describe which method to use and when to consider model performance as acceptable.

Predicted-to-observed PK parameter ratios. A PK parameter, such as V_d or CL, is accurately predicted if the predicted parameter falls within a predefined acceptance range of the observed value. There remains a lack of consistency in literature with regard to what range to use as generally acceptable.[50] The most commonly applied criterion is the twofold acceptance range (predicted/observed ratio between 0.5 and 2). A wider acceptance range can be considered for drugs characterized by a high interindividual variability in PKs. Although, it is an ongoing debate if this criterion is strict enough for drugs with low clinical variability, as known from highly powered clinical studies and for drugs with a small therapeutic window.[62] Therefore, more stringent ranges are considered, such as the 1.5-fold and the 1.25-fold (the bioequivalence) ranges. Templeton and colleagues[63] considered the 1.5-fold to be adequate, although they argue that, due to large clinical variability, a larger margin is more appropriate when predicting PKs in neonates.[64]

In addition, other predefined criteria have been developed which can be considered. For example, the 99.998% confidence interval criterion which takes the sample size and coefficient of variation into account.[62] Or, for example, the Guest criterion for the assessment of simulated DDIs.[65]

MODEL APPLICATION

When there is sufficient confidence in the model to accurately predict pediatric PKs, the model can be applied to prospectively address the question of interest (see Modeling objective). Untested dosing scenarios can be simulated to evaluate what the most optimal and practical dose should be. Three key aspects have to be taken into consideration: the required exposure margin to ensure an effective and safe dose (i.e., the therapeutic window), differences in studied populations that may affect model assumption, and the practicality of the proposed dosing strategy.

When establishing an MID, it is essential to know which plasma concentrations are effective and safe. For some drugs, it is aimed to reach a certain exposure target (e.g., trough plasma concentration (C_{trough}) below x or AUC/MIC above y) or to maintain within a therapeutic window to guide dosing. A second option is conducting exposure matching, based on data from another population. We elaborate on these two scenarios below.

Therapeutic window and exposure target is available

As previously mentioned, a known exposure target allows us to link plasma (or tissue) exposure with a desired clinical effect. For some drugs, a certain C_{trough} or C_{max} level might be related to efficacy or safety (i.e., therapeutic window), whereas other drugs may have a specific exposure-response relationship, such as an AUC/MIC. Data from toxicity studies and/or case reports can be helpful to determine the highest exposure level that may still be considered safe. Virtual clinical trials with untested dosing scenarios can be performed to evaluate which dosing strategy provides the most optimal exposure. Currently, available dosing recommendations should be tested first to confirm if existing recommendations result in accurate exposure. P-PBPK applied in this way provides an additional digital piece of evidence to confirm current dosing recommendation. If simulations demonstrate that exposure can be improved by adjusting the dose, dosing interval, or perhaps the route of administration, this should then be discussed with clinicians to potentially update the current recommendation. Granted that no dosing recommendation is available yet for the specific age range or indication, dosing strategies for other ages or indications can be simulated first to subsequently adjust the dosing strategy based on exposure matching (see point Pediatric and preterm model verification).

Ideally, a therapeutic window and exposure target is known for the intended pediatric age range as extrapolating a PK/PD relationship from adults to children is often assumed from a practical standpoint, although required exposure in children may differ from that in adults due to differences in pathophysiology, disease manifestation, and disease progression, as well as differences in response to intervention.[66,67] In those cases, potential concerns regarding the assumptions should be mentioned and evaluated. Note that an exposure target for another indication might not be suitable for the indication of interest, especially if the mechanism of action between indications is different. Extrapolating exposure targets for efficacy from other indications is hence not recommended, unless other evidence suggests it is suitable, for example, preclinical studies. Yet, a therapeutic window for another indication can be useful, for example, by applying the known maximum safe concentration of the drug to the scenario of interest (assuming that the disease state does not affect risk or severity of toxicity). Modeling results should be presented as plasma-concentration time profiles with the PK target indicated.

Exposure matching in absence of defined therapeutic window

If there is no PK target and no therapeutic window to aim for, the MID can be established based on exposure matching, that is, aim for drug exposure in the population of interest to be equal to

exposure in a population for which exposure is considered effective and safe. In case of exposure matching based on AUC, ensure that peak exposure is considered safe and adjust the dosing strategy if needed (lower doses with shorter dosing intervals). This approach assumes a similar exposure-response relationship between the populations.

When the established MID is different from the current dosing recommendation, clinical experts should evaluate the proposed dose, taking into account PBPK model credibility, while considering other available data and balancing the benefits with the potential risks. A standardized framework for clinicians is needed to guide clinical implementation of an MID informed by PBPK. A framework to implement dosing based on population-PK analysis has been proposed previously and can be used as a starting point.[68]

CONCLUSION

Physiologically-based pharmacokinetic modeling is an attractive tool to establish MID for pediatric clinical care. Contemporary pediatric physiology models are scientifically well-founded and are continuously improved to better quantify developmental changes. PBPK model predictions increase our knowledge with respect to drug PKs and may guide dosing in an ethically acceptable manner, which is less costly, less time-consuming, and arguably more informative compared with conducting pediatric clinical trials. Pragmatic PBPK modeling has come into reach because of the increasing number of established compound and population models. This tutorial provides a structured overview of important considerations when conducting pragmatic PBPK modeling studies and provide a path toward implementing PBPK-based MID in pediatric clinical care. Key points of attention at every step of the modeling process were discussed. We hope this enables modelers, researchers, and clinicians to understand and more widely utilize PBPK modeling for pediatric drug dosing.

We highlighted several key aspects of pragmatic PBPK modeling. Assumptions are often being made during initial model parameterization and the user might not be aware of this. In addition, there is currently no consensus on when to consider model performance acceptable, let alone a consensus on the (quantitative) level of confidence needed for model extrapolation. Furthermore, the model-informed dose is generally established based on simulations of healthy pediatric virtual population, whereas the condition of the real-world patients (e.g., disease or treatment) may ask for an adjusted dose. Additionally, to use this approach to the fullest, published PBPK models should follow an open-science practice with models accessible (e.g., through online repositories) for researchers and healthcare providers to evaluate and apply.

Conducting pragmatic PBPK modeling using this tutorial is the first step toward implementation of an MID in dosing guidelines. Review of the suggested dose in the context of safety and efficacy, by expert PBPK modelers, pharmacologists, physicians, and regulatory experts, is subsequently needed. We suggest that for each MID a report covering all the elements of this tutorial (background information, model requirements, model verification, and model application), is created and be available for use in multidisciplinary working groups. We also suggest that after implementation of a PBPK-based MID, re-evaluation of the MID should be performed regularly once new clinical data or new data on the underlying ADME processes that impact PKs, emerges.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The authors thank Dr Ping Zhao for useful discussions that improved the manuscript.

FUNDING

This publication is based on research funded by the Bill & Melinda Gates Foundation (INV-001822). The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the Bill & Melinda Gates Foundation.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

1. The State of Paediatric Medicines in the EU commission report: 10 years of the EU Paediatric Regulation. <https://ec.europa.eu/health/system/files/2017-11/2017_childrensmedicines_report_en_0.pdf> (2017).
2. Leil, T.A., Zee, P., Suryawanshi, S., Male, C. & Portman, R. Quantitative extrapolation: an approach to validation of adult drug efficacy in pediatric subjects. *Ther. Innov. Regul. Sci.* **47**, 557–565 (2013).
3. Zhang, X. *et al*. Application of PBPK modeling and simulation for regulatory decision making and its impact on US prescribing information: an update on the 2018-2019 submissions to the US FDA's Office of Clinical Pharmacology. *J. Clin. Pharmacol.* **60**(Suppl 1), S160–S178 (2020).
4. Johnson, T.N., Small, B.G. & Rowland, Y.K. Increasing application of pediatric physiologically based pharmacokinetic models across academic and industry organizations. *CPT Pharmacometrics Syst. Pharmacol.* **11**, 373–383 (2022).
5. Adiwidjaja, J., Boddy, A.V. & McLachlan, A.J. Implementation of a physiologically based pharmacokinetic modeling approach to guide optimal dosing regimens for imatinib and potential drug interactions in Paediatrics. *Front. Pharmacol.* **10**, 1672 (2019).
6. Zhang, Y., Zhao, S., Wang, C., Zhou, P. & Zhai, S. Application of a physiologically based pharmacokinetic model to characterize time-dependent metabolism of voriconazole in children and support dose optimization. *Front. Pharmacol.* **12**, 636097 (2021).
7. Neeli, H., Hanna, N., Abduljalil, K., Cusumano, J. & Taft, D.R. Application of physiologically based pharmacokinetic-pharmacodynamic modeling in preterm neonates to guide gentamicin dosing decisions and predict antibacterial effect. *J. Clin. Pharmacol.* **61**, 1356–1365 (2021).
8. Hornik, C.P., Wu, H., Edginton, A.N., Watt, K., Cohen-Wolkowiez, M. & Gonzalez, D. Development of a pediatric physiologically-based pharmacokinetic model of clindamycin using opportunistic pharmacokinetic data. *Clin. Pharmacokinet.* **56**, 1343–1353 (2017).
9. Zheng, L., Xu, M., Tang, S.W., Song, H.X., Jiang, X.H. & Wang, L. Physiologically based pharmacokinetic modeling of oxycodone in children to support pediatric dosing optimization. *Pharm. Res.* **36**, 171 (2019).
10. Jo, H., Pilla Reddy, V., Parkinson, J., Boulton, D.W. & Tang, W. Model-informed pediatric dose selection for dapagliflozin by

incorporating developmental changes. *CPT Pharmacometrics Syst. Pharmacol.* **10**, 108–118 (2021).
11. Verscheijden, L.F.M. *et al*. Chloroquine dosing recommendations for pediatric COVID-19 supported by modeling and simulation. *Clin. Pharmacol. Ther.* **108**, 248–252 (2020).
12. Freriksen, J.J.M., van der Heijden, J.E.M., de Hoop-Sommen, M.A., Greupink, R. & de Wildt, S.N. Physiologically based pharmacokinetic (PBPK) model-informed dosing guidelines for pediatric clinical care: a pragmatic approach for a special population. *Paediatr. Drugs*. **25**, 5–11 (2023).
13. van der Heijden, J.E.M. *et al*. Feasibility of a pragmatic PBPK modeling approach: towards model-informed dosing in pediatric clinical care. *Clin. Pharmacokinet.* **61**, 1705–1717 (2022).
14. European Medicines Agency Reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. <https://www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation> (2018). Accessed August 12, 2022.
15. US Food and Drug Administration Physiologically Based Pharmacokinetic Analyses - Format and Content Guidance for Industry <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/physiologically-based-pharmacokinetic-analyses-format-and-content-guidance-industry>. (2018) Accessed August 12, 2022.
16. Maharaj, A.R. & Edginton, A.N. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT Pharmacometrics Syst. Pharmacol.* **3**, e150 (2014).
17. van der Zanden, T.M. *et al*. Off-label, but on-evidence? A review of the level of evidence for pediatric pharmacotherapy. *Clin. Pharmacol. Ther.* **112**, 1243–1253 (2022).
18. WHO Paediatric ARV dosing tool. <https://paedsarvdosing.org/>. [18-08-2022].
19. Rowland Yeo, K. & Venkatakrishnan, K. Physiologically-based pharmacokinetic models as enablers of precision dosing in drug development: pivotal role of the human mass balance study. *Clin. Pharmacol. Ther.* **109**, 51–54 (2021).
20. Mooij, M.G. *et al*. Successful use of [(14)C]paracetamol microdosing to elucidate developmental changes in drug metabolism. *Clin. Pharmacokinet.* **56**, 1185–1195 (2017).
21. Aldridge, A., Aranda, J.V. & Neims, A.H. Caffeine metabolism in the newborn. *Clin. Pharmacol. Ther.* **25**, 447–453 (1979).
22. Nielsen, E.I., Cars, O. & Friberg, L.E. Pharmacokinetic/pharmacodynamic (PK/PD) indices of antibiotics predicted by a semimechanistic PKPD model: a step toward model-based dose optimization. *Antimicrob. Agents Chemother.* **55**, 4619–4630 (2011).
23. Jacqmin, P. *et al*. Modelling response time profiles in the absence of drug concentrations: definition and performance evaluation of the K-PD model. *J. Pharmacokinet. Pharmacodyn.* **34**, 57–85 (2007).
24. Ezuruike, U. *et al*. Guide to development of compound files for PBPK modeling in the Simcyp population-based simulator. *CPT Pharmacometrics Syst. Pharmacol.* **11**, 805–821 (2022).
25. Open Systems Pharmacology. <https://docs.open-systems-pharmacology.org/working-with-pk-sim/pk-sim-documentation/pk-sim-compounds-definition-and-work-flow>. [5 July 2023].
26. Frechen, S. & Rostami-Hodjegan, A. Quality assurance of PBPK modeling platforms and guidance on building, evaluating, verifying and applying PBPK models prudently under the umbrella of qualification: why, when, what, how and by whom? *Pharm. Res.* **39**, 1733–1748 (2022).
27. Verscheijden, L.F.M., Koenderink, J.B., Johnson, T.N., de Wildt, S.N. & Russel, F.G.M. Physiologically-based pharmacokinetic models for children: starting to reach maturation? *Pharmacol. Ther.* **211**, 107541 (2020).
28. Yellepeddi, V., Rower, J., Liu, X., Kumar, S., Rashid, J. & Sherwin, C.M.T. State-of-the-art review on physiologically based pharmacokinetic modeling in pediatric drug development. *Clin. Pharmacokinet.* **58**, 1–13 (2019).
29. T'jollyn, H., Vermeulen, A. & Van Bocxlaer, J. PBPK and its virtual populations: the impact of physiology on pediatric pharmacokinetic predictions of tramadol. *AAPS J.* **21**, 8 (2018).
30. Thakur, A., Parvez, M.M., Leeder, J.S. & Prasad, B. Ontogeny of drug-metabolizing enzymes. *Methods Mol. Biol.* **2342**, 551–593 (2021).
31. 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).
32. Cleary, Y. *et al*. Model-based drug-drug interaction extrapolation strategy from adults to children: Risdiplam in pediatric patients with spinal muscular atrophy. *Clin. Pharmacol. Ther.* **110**, 1547–1557 (2021).
33. Cockcroft, D.W. & Gault, M.H. Prediction of creatinine clearance from serum creatinine. *Nephron* **16**, 31–41 (1976).
34. Schwartz, G.J., Haycock, G.B., Edelmann, C.M. Jr. & Spitzer, A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* **58**, 259–263 (1976).
35. Schwartz, G.J., Brion, L.P. & Spitzer, A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr. Clin. North Am.* **34**, 571–590 (1987).
36. Levey, A.S., Bosch, J.P., Lewis, J.B., Greene, T., Rogers, N. & Roth, D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann. Intern. Med.* **130**, 461–470 (1999).
37. van Rossum, L.K., Mathot, R.A., Cransberg, K., Zietse, R. & Vulto, A.G. Estimation of the glomerular filtration rate in children: which algorithm should be used? *Pediatr. Nephrol.* **20**, 1769–1775 (2005).
38. Panteghini, M., Myers, G.L., Miller, W.G. & Greenberg, N. The importance of metrological traceability on the validity of creatinine measurement as an index of renal function. *Clin. Chem. Lab. Med.* **44**, 1287–1292 (2006).
39. Rhodin, M.M. *et al*. Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr. Nephrol.* **24**, 67–76 (2009).
40. Hayton, W.L. Maturation and growth of renal function: dosing renally cleared drugs in children. *AAPS PharmSci* **2**, E3–E28 (2000).
41. Smeets, N.J.L., IntHout, J., van der Burgh, M.J.P., Schwartz, G.J., Schreuder, M.F. & de Wildt, S.N. Maturation of GFR in term-born neonates: an individual participant data meta-analysis. *J. Am. Soc. Nephrol.* **33**, 1277–1292 (2022).
42. Berezhkovskiy, L.M. Volume of distribution at steady state for a linear pharmacokinetic system with peripheral elimination. *J. Pharm. Sci.* **93**, 1628–1640 (2004).
43. Rodgers, T., Leahy, D. & Rowland, M. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *J. Pharm. Sci.* **94**, 1259–1276 (2005).
44. Poulin, P. & Theil, F.P. Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanism-based prediction of volume of distribution. *J. Pharm. Sci.* **91**, 129–156 (2002).
45. Schmitt, W. General approach for the calculation of tissue to plasma partition coefficients. *Toxicol. In Vitro* **22**, 457–467 (2008).
46. PubChem. <https://pubchem.ncbi.nlm.nih.gov/>. [5 July 2023].
47. DrugBank. <https://go.drugbank.com/>. [5 July 2023].
48. Peters, S.A. & Dolgos, H. Requirements to establishing confidence in physiologically based pharmacokinetic (PBPK) models and overcoming some of the challenges to meeting them. *Clin. Pharmacokinet.* **58**, 1355–1371 (2019).
49. Rostami-Hodjegan, A. Reverse translation in PBPK and QSP: going backwards in order to go forward with confidence. *Clin. Pharmacol. Ther.* **103**, 224–232 (2018).
50. Sager, J.E., Yu, J., Ragueneau-Majlessi, I. & Isoherranen, N. Physiologically based pharmacokinetic (PBPK) modeling and simulation approaches: a systematic review of published models, applications, and model verification. *Drug Metab. Dispos.* **43**, 1823–1837 (2015).

51. Michelet, R., Van Bocxlaer, J., Allegaert, K. & Vermeulen, A. The use of PBPK modeling across the pediatric age range using propofol as a case. *J. Pharmacokinet. Pharmacodyn.* **45**, 765–785 (2018).
52. Kuepfer, L. *et al*. Applied concepts in PBPK modeling: how to build a PBPK/PD model. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 516–531 (2016).
53. Fuhr, L.M., Marok, F.Z., Hanke, N., Selzer, D. & Lehr, T. Pharmacokinetics of the CYP3A4 and CYP2B6 inducer carbamazepine and its drug-drug interaction potential: a physiologically based pharmacokinetic modeling approach. *Pharmaceutics.* **13**, 270 (2021).
54. Blanchet, B., Jullien, V., Vinsonneau, C. & Tod, M. Influence of burns on pharmacokinetics and pharmacodynamics of drugs used in the care of burn patients. *Clin. Pharmacokinet.* **47**, 635–654 (2008).
55. van den Broek, M.P., Groenendaal, F., Egberts, A.C. & Rademaker, C.M. Effects of hypothermia on pharmacokinetics and pharmacodynamics: a systematic review of preclinical and clinical studies. *Clin. Pharmacokinet.* **49**, 277–294 (2010).
56. Shekar, K., Fraser, J.F., Smith, M.T. & Roberts, J.A. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. *J. Crit. Care* **27**, 741.e9–741.e18 (2012).
57. Ince, I. *et al*. Predictive performance of physiology-based pharmacokinetic dose estimates for pediatric trials: evaluation with 10 Bayer Small-molecule compounds in children. *J. Clin. Pharmacol.* **61**(Suppl 1), S70–s82 (2021).
58. 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).
59. Stephenson, T. How children's responses to drugs differ from adults. *Br. J. Clin. Pharmacol.* **59**, 670–673 (2005).
60. Yamamoto, Y. *et al*. Predicting drug concentration-time profiles in multiple CNS compartments using a comprehensive physiologically-based pharmacokinetic model. *CPT Pharmacometrics Syst. Pharmacol.* **6**, 765–777 (2017).
61. Maharaj, A.R. *et al*. Use of normalized prediction distribution errors for assessing population physiologically-based pharmacokinetic model adequacy. *J. Pharmacokinet. Pharmacodyn.* **47**, 199–218 (2020).
62. Abduljalil, K., Cain, T., Humphries, H. & Rostami-Hodjegan, A. Deciding on success criteria for predictability of pharmacokinetic parameters from in vitro studies: an analysis based on in vivo observations. *Drug Metab. Dispos.* **42**, 1478–1484 (2014).
63. Templeton, I.E., Jones, N.S. & Musib, L. Pediatric dose selection and utility of PBPK in determining dose. *AAPS J.* **20**, 31 (2018).
64. Allegaert, K. & van den Anker, J.N. Clinical pharmacology in neonates: small size, huge variability. *Neonatology* **105**, 344–349 (2014).
65. Guest, E.J., Aarons, L., Houston, J.B., Rostami-Hodjegan, A. & Galetin, A. Critique of the two-fold measure of prediction success for ratios: application for the assessment of drug-drug interactions. *Drug Metab. Dispos.* **39**, 170–173 (2011).
66. US Food and Drug Administration Guidance for Industry: Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications. <https://www.fda.gov/media/71277/download>. (2003) [02-01-2023].
67. European Medicines Agency Reflection paper on the use of extrapolation in the development of medicines for paediatrics. <https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf> (2018). January 01, 2023.
68. Hartman, S.J.F. *et al*. A new framework to implement model-informed dosing in clinical guidelines: piperacillin and amikacin as proof of concept. *Front. Pharmacol.* **11**, 592204 (2020).