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REVIEW ARTICLE

Pharmacokinetic–Pharmacodynamic Modeling in Pediatric Drug Development, and the Importance of Standardized Scaling of Clearance

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Abstract Pharmacokinetic/pharmacodynamic (PKPD) modeling is important in the design and conduct of clinical pharmacology research in children. During drug development, PKPD modeling and simulation should underpin rational trial design and facilitate extrapolation to investigate efficacy and safety. The application of PKPD modeling to optimize dosing recommendations and therapeutic drug monitoring is also increasing, and PKPD model-based dose individualization will become a core feature of personalized medicine. Following extensive progress on pediatric PK modeling, a greater emphasis now needs to be placed on PD modeling to understand age-related changes in drug effects. This paper discusses the principles of PKPD modeling in the context of pediatric drug development, summarizing how important PK parameters, such as clearance (CL), are scaled with size and age, and highlights a standardized method for CL scaling in children. One standard scaling method would facilitate comparison of PK parameters across multiple studies, thus increasing the utility of existing PK models and facilitating optimal design of new studies.

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Key Points

Pharmacokinetic/pharmacodynamic (PKPD) modeling is important in the design and conduct of clinical pharmacology research in children, and the so-called 'population' approach is suitable for rich or sparse data in terms of the number of samples per subject

The utility of pediatric PK models can be increased by using a standardized approach to scaling: a suggested method for scaling clearance (CL) is a combination of allometric weight scaling with a sigmoid function to account for organ maturation. This should be used a priori, as a 'base' approach, allowing the effects of age and size to be delineated from other patient-specific factors, such as disease state and organ (dys)function

When determining the pediatric dose, instead of directly scaling the dose from adults to children, the pediatric PK parameter estimates should be obtained from a PK model with a standardized scaling approach in order to avoid the use of arbitrary cut-off values (of age/weight) according to a specific (non-standardized) CL-scaling formula

Significant progress has recently been made on pediatric PK modeling; a greater emphasis now needs to be placed on PD modeling to understand age-related changes in drug effects

PKPD model-based dose individualization is becoming increasingly popular as the age of personalized medicine dawns

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1 Introduction

During the evolution of modern drug development, pediatrics and neonatology were largely neglected, rendering children and infants 'therapeutic orphans' [1, 2]. However, in recent years there has been an increase in research activity to support the development of evidence-based pharmacotherapy for children stimulated by the advent of new legislation to mandate licensing for new medicinal products in this population [3, 4]. Pharmacokinetic/pharmacodynamic (PKPD) modeling and simulation (M&S) play a pivotal role in pediatric drug development through supporting rational trial design and increasingly replacing traditional trials through extrapolation of efficacy and safety [5–7]. Furthermore, the application of PKPD modeling to optimize dosing recommendations and therapeutic drug monitoring (TDM) strategies is also increasingly recognized. Historically, children were originally treated as 'small adults', i.e. the dose was simply scaled down per linear weight, leading potentially to overdosing in very small children, especially neonates, as their kidneys and liver were not yet fully developed, often resulting in slower drug elimination [8]. As awareness of developmental pharmacology subsequently expanded, the physiological differences in drug handling between children and adults were emphasized, leading to the notion that 'children are not small adults' [9]. However, rather than dichotomizing adult and pediatric patients, recognition that maturation is a continuous process has since led to acknowledgment of the need to quantify differences and understand similarities across the age range with appropriate scaling. This paper discusses the principles of PKPD modeling in the context of pediatric drug development, and highlights the importance and benefits of using one standardized method for scaling clearance (CL) in children.

2 Pediatric Drug Development: Background and Legislation

In many regions, including the US and Europe, regulations requiring pharmaceutical companies to demonstrate both safety and efficacy of their products prior to marketing were introduced following the tragic events relating to thalidomide use during the 1960s [10]. Despite the fact that infants were the main victims of thalidomide's teratogenic effects, the resultant drug legislation was not specifically targeted towards children or neonates [1]. This meant that unlicensed and off-label use of medicines has remained unavoidably commonplace in pediatrics and neonatology, together with its associated risks [11–14]. However, in recent years, specific legislation has come into effect that enshrines pediatric medicines research in law for new medicinal products licensed within the relevant jurisdictions [15, 16]. Some key landmarks in these developments are outlined in Table 1.

In both the European Union (EU) and the US, the introduction of such legislation has necessitated the consideration of children and neonates earlier during the drug development process. During the last 20 years, the use of M&S to support pharmacological research in children, as well as adults, has also advanced significantly. The techniques of M&S may be applied in various contexts and are not solely limited to PKPD studies (where they are often known as pharmacometrics); these techniques are discussed further below. It is important to note that the applications and benefits of M&S in drug development and postmarketing drug research are often at risk of being underutilized [17], especially in circumstances when there may be limited expertise or if there is ineffective dialogue between those specialized in modeling (e.g. 'pharmacometricians' [18, 19]) and those directly involved in patient care, i.e. clinicians and pharmacists. Fortunately, the benefits of applying quantitative pharmacological methods in clinical practice are now more widely appreciated [20], in addition to their key roles in research and drug development [21–25]. To reflect this, there is also a growing number of experts in M&S within regulatory agencies [26–28].

2.1 Extrapolating the Dose from Adults to Children

Before considering the pediatric population during drug development, PKPD data are normally first available from adult subjects, either healthy volunteers and/or patients. This then generates questions surrounding the extrapolation of PKPD information to children, regarding when one can appropriately use extrapolation techniques [29] and what information can be safely extrapolated.

Extrapolation can be defined as [abbreviated] "Extending information and conclusions available from studies in one or more subgroups of the patient population (source population) […] to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information […] to reach conclusions for the target population […]" [30].

Before undertaking extrapolation exercises, various distinct aspects of pharmacology must be considered, including the following.

1. Pharmacokinetics: Absorption, distribution, metabolism, elimination (ADME), and the influence of developmental pharmacology and ontogeny on the drug's PK profile in children of different ages. The

Table 1 Key landmarks in pediatric medicines regulation

Year	Regulation	Impact
1997	US FDA Modernization Act (FDAMA)	This act presented the financial incentive of an additional 6 months of market exclusivity to companies undertaking required pediatric studies [15]
1998	US FDA Pediatric Rule	This rule permitted companies to label medicines for use in children based on extrapolation of efficacy from adult trial data, together with pediatric PKPD and safety data [160]
2002 (and 2007)	US Best Pharmaceutical for Children Act (BPCA)	Framework for pediatric research in both on- and off-patent drugs [161]
2003	US Pediatric Research Equity Act (PREA)	Sponsors required to undertake clinical studies in children for new medicines and biological products [161]
2007	EU Pediatric Regulation	Introduction of new legislation in the European Union mandating pediatric medicines research for new medicinal products [16]
2012	US Food and Drug Administration Safety and Innovation Act (FDASIA)	BPCA and PREA became permanent in US Law [162]

PKPD pharmacokinetic/pharmacodynamic

impact of comorbidities, e.g. renal failure [31], on drug disposition may also need to be evaluated, where relevant.

2. Pharmacodynamics (including both efficacy and toxicity): Consideration of host developmental and receptor pharmacology, which can affect both the desired drug effect, through the principal mode of action, and any off-target effects, which may be desirable (e.g. the anti-inflammatory activity of macrolide antibiotics [32]), neutral (i.e. of no clinically important consequence), or toxic. When the target receptor is in another organism, e.g. the drug target located within the pathogen in the case of anti-infective therapies, consideration must also be given as to whether the target pathogen's resistance profile is likely to be the same in neonates and children as in adults.

3. Formulations: Pediatric age-appropriate, formulation-related issues should be addressed as early as possible [33], with consideration of a number of factors such as any potential for excipient-related toxicity [34, 35], and also palatability and the development of child-friendly dosage regimens where feasible, both of which will affect compliance in children [36–38].

M&S can contribute to each of the assessments outlined above; ranging from dose selection for neonatal/pediatric clinical studies [39], to investigating the impact of altered dosing regimens that would fit in better with a child's daily routine. Thus, the appropriate use of M&S for extrapolation approaches is of particular significance in pediatric drug development [40].

For determining when extrapolation is or is not appropriate, a useful point of reference is the US FDA Pediatric Study Decision Tree, shown in Fig. 1 (adapted), which has been developed for supporting decision making regarding extrapolation during pediatric drug development [41, 42].

This decision tree highlights the need to evaluate different issues, including the following.

1. Natural history of disease progression in children/adults, and response to therapeutic intervention.

2. Likely exposure–response profile: Is it sufficient to simply target the same drug exposure (e.g. with respect to the area under the curve (AUC) in the PK profile, once this has been scaled appropriately; see further details below)?

3. Suitability of the pharmacodynamic measures and whether these are applicable to children: Is the PKPD index likely to be the same? For example, during antimicrobial therapy, typical PKPD indices, such as the peak concentration (C_{max}) for aminoglycoside therapy, are used in both adult and pediatric populations [43, 44], but, for some medications/conditions (such as pulmonary hypertension in neonates [45]), different pediatric PD measures are required.

The science of extrapolation is a rapidly evolving area, with many aspects that warrant detailed research [42, 46–49]. In future, it is likely that there will be further guidance about related issues, such as the appropriateness of extrapolation of data between agents within the same therapeutic class, and how to extrapolate from in vivo models to neonates for conditions that do not have a counterpart within the adult population [50]. Overall, extrapolation should now be viewed as an ethical requirement for pediatric drug development since it can reduce the chance of undertaking unnecessary research and support the design of those pediatric studies that are required [42]. Accordingly, this important topic has been the focus of
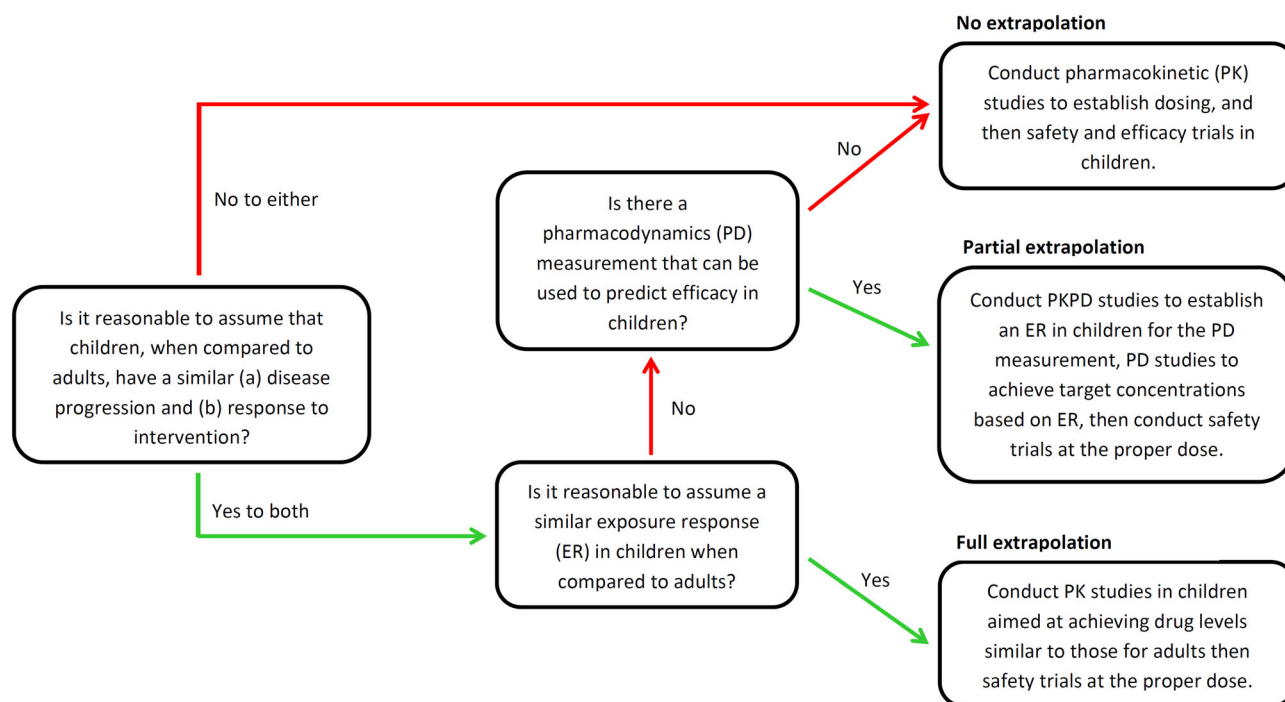
Fig. 1 Decision tree for pediatric studies. Adapted from Dunne et al. [42]. *PKPD* pharmacokinetic/pharmacodynamic

recent new regulatory documents from both the European Medicines Agency [51] and the International Council on Harmonization [52].

2.2 Different Levels of Evidence Required

In different circumstances, varying levels of PKPD and safety data may be required, depending on the particular drug concerned and the availability of existing, relevant data in pediatric and neonatal populations. It is important to assess both the quantity and quality of the PKPD data that are available in particular pediatric populations [53]. There are a number of regulatory guidelines that provide advice to pharmaceutical companies on these topics (for example, see [53–58]). Some key issues can remain in the 'gray' areas; for example, the best way to do sample size calculations for pediatric PKPD studies that will use population modeling for the analysis. Previously, Tam et al. investigated the sample size required to generate robust PK predictions when using population modeling with Monte Carlo simulations to predict antimicrobial PK variability [59]. To obtain reasonably robust predictions, it was recommended that a non-parametric model derived from a sample population size of at least 50 subjects was needed as the input information [59]. However, limited data are currently available to support evidence-based target setting within specific subpopulations, such as neonates born at varying stages of prematurity and with varying degrees of organ dysfunction. Early consultation with pediatric or neonatal clinical pharmacologists and pharmacists is advisable during the protocol development stage to address these challenges. Pragmatic considerations are also important to ensure the feasibility of study targets, with consideration of whether they are realistically achievable within the desired time frames, as recruitment rates into pediatric trials (including simple PK studies) are often surprisingly low [60, 61]. The FDA have issued specific guidance on pediatric PK study sample size calculation as follows: "The study must be prospectively powered to target a 95% confidence interval (CI) within 60 and 140% of the geometric mean estimates of clearance and volume of distribution for DRUG NAME in each pediatric sub-group with at least 80% power" [62], and Stockmann et al. published recommendations on how to undertake such calculations [63]. It is important to recognize that such sample size calculations will inevitably be affected by uncertainty of the expected pharmacokinetic parameters in the target population, and therefore adaptive optimal designs may have a role to play in target refinement during study delivery [64]. Sample size might also depend on the richness of the data, and, in studies where rich sampling is usually not possible (e.g. neonatal studies), optimal design can prove useful by providing the most informative time points for sampling, thus reducing the number of samples required per subject enrolled [65]. Using optimal design to identify the most informative sampling times in each pediatric age group can, at the same time, also help to increase the power of the PKPD analysis.

3 Rationale for Using Modeling

There are numerous advantages to using a model-based approach over the (traditional) data summary approach (i.e. calculate AUC, C_{max}, etc) for PK or PD studies in children [66]. For example, non-linear mixed-effects modeling facilitates the analysis of sparse, unbalanced datasets, which are common in neonatal and pediatric research settings, where each individual may only contribute a small number of samples, and sample timing/number of samples can vary between patients—as, for example, in studies with opportunistic sampling [23, 67, 68]. Furthermore, models can incorporate factor-relevant covariates, such as age and weight, which enable us to evaluate the developmental differences between adults and children, in addition to ontogeny and pharmacogenetic factors [23]. The developed model can also account for the whole concentration–time course, and hence can readily be used as a link with the effect (PD).

A detailed description of the statistical and mathematical aspects of PKPD modeling is beyond the scope of this review, but a brief summary of typical modeling methods for analyzing PKPD data is provided in Table 2 [67].

4 Specific Issues in Pediatric Pharmacokinetic/ Pharmacodynamic (PKPD) Modeling

4.1 Scaling of Pharmacokinetics

4.1.1 Different Approaches for Scaling Pharmacokinetics

Children, especially infants, are smaller, weigh less, and have a higher proportion of total body water and lower proportion of body fat compared with adults. Furthermore, key organ function, specifically kidney and liver function, is immature in newborns and infants, resulting in a lower glomerular filtration rate (GFR) and a distinct hepatic enzyme activity profile. Membrane-bound drug transporters also vary with age [69]. These numerous physiological differences between adults and children, particularly infants, contribute to PK processes, and consequent age- and size-related differences in PK parameters [70]. Therefore, PK parameters cannot simply be scaled linearly from adults to children; instead, approaches such as allometric scaling, physiologically-based pharmacokinetic (PBPK) models [71], and systems pharmacology modeling [72] should be used [73].

PBPK models are represented by a complex system of equations with parameters that incorporate biological knowledge of physiological blood flows, anatomical organ structures, and also tissue and organ volumes [74]. PBPK models can be used to predict first-in-man drug doses (prior to human exposure) [75], first-in-children doses [76], and, more recently, for drug–drug interaction studies [77], but have also been suggested for scaling PK to children [78, 79]. If the aim of a PBPK model is extrapolation to the pediatric population, it must either firstly describe the adult data well and include data on all developmental changes affecting drug pharmacokinetics [80, 81], or, alternatively, an existing PBPK model for children of a certain age and medical condition can be used, together with the physicochemical properties of the studied drug. However, extrapolating across all age groups might be difficult for some physiological spaces, for example brain and bone marrow [80]. It can also be challenging to obtain sufficient in vitro data for some compounds, which could then lead to poor

Table 2 Overview of core pharmacokinetic analytical methods [67]

Method	Description	Comments
Naive pooled data approach	All PK data from the study are pooled and analyzed as if from one individual	The analysis does not incorporate the fact that the data arise from individuals with between-subject variability, and can give biased parameter estimates; it can be used in unbalanced study designs but will overestimate variability and can lead to biased parameter estimates
Naive average data approach	The mean drug concentration at each time point in the PK study is calculated, based on the data at that time point contributed by all participants. The mean value at each sampling time is then used to estimate the PK parameters of interest	This simplistic approach is popular but is unreliable and limited because it does not consider inter- or intraindividual variability, and therefore underestimates variability. It is only suitable for a balanced study design
Two-stage approach	The PK parameters are first estimated for each individual, then the variance of these parameter estimates is calculated	This method is attractive because it is mathematically straightforward, but requires rich individual-level data
Non-linear mixed effect modeling (NLME)	All study data are fitted simultaneously in one model, but the PK parameters are able to vary between individuals	This approach has become standard practice because it provides unbiased parameter estimates through simultaneous quantification of parameter-level interindividual variability, and observation-level residual variability

PK pharmacokinetic

predictive performance [82]. Some authors have fitted PBPK models to PK data to overcome this [83, 84]; however, this approach is not yet widely used in pediatric research, but is growing in application and can be used to update or refine the PBPK model. Although the validation requirements for PBPK models are not yet as well defined as, for example, those for population PKPD modeling, the average fold error is often used as a guiding metric for validation [85, 86].

Systems pharmacology models are based on a network of nodes (or functional elements), with functional interactions between them. Recently, these models have been suggested to be useful for describing disease progression and complex drug action patterns [72].

An alternative to extrapolating PK from adults to children is to perform model-based meta-analysis of existing pediatric data [73], or an empirical analysis of the observed pediatric drug PK data [73], where characteristics of patients can be used as covariates to help explain and describe the ontogeny of a PK parameter. These two approaches are especially useful when, for example, designing a new clinical trial (to e.g. test a new dosing regimen) in a similar pediatric population. Since pharmacological effects of many drugs are driven by drug exposure (AUC), which is indirectly proportional to CL, we usually focus on scaling CL. As CL changes as humans grow and age/mature, models need to account for these two, correlated processes.

For drugs that are orally administered, the influences of age-appropriate formulations and developmental differences in bioavailability on pharmacokinetics also need to be considered, which are discussed in detail elsewhere [87]; these factors can also be taken into account with model-based approaches to investigate pediatric PK.

4.1.2 Body Size

Almost 70 years ago, Crawford et al. noted that using body surface area (BSA) is preferred over linear weight for predicting doses [88]. Decades later, it was suggested that a so-called allometric approach (Eq. 1), which scales metabolic processes with body size, could also be used to explain changes in drug CL [89]:

$$y_i = a \cdot WT_i^b, \tag{1}$$

where y_i is the individual subject's body function of interest (that is being predicted), WT is the individual's body weight in kilograms, a is the allometric constant, which assumes the value of y when WT = 1 kg, and b is the allometric exponent ($b < 1$ indicates that the body function increases slower with body size than weight).

Hereafter, we use the term allometric scaling to refer to allometric scaling of CL.

Historically, although studied for almost a century, there has been no agreement on which value of the allometric exponent to use, but generally values between 0.63 and 0.78 have been suggested. For example, in the 1930s, Benedict proposed the use of 0.67 since it was found that the basal metabolic rates scale best with BSA, which is approximately $WT^{0.67}$ [90]. Around the same time, Kleiber looked at 13 different species of mammals with a wide weight range (0.15–679 kg) and concluded that the value of the allometric exponent should be 0.75 [91]. However, he also noticed that the value of the exponent (0.67 or 0.75) only altered predictions if the difference between the subjects' weight was at least ninefold [92]. More recently, GFR was found to scale with weight raised to the power of 0.63 [93], and hepatic blood flow with $WT^{0.78}$ [94]. In a recent meta-analysis of almost 500 PK studies, McLeay et al. [95] found that, when estimated, the median value of the allometric exponent was 0.65 (range − 1.2 to 2.2), but the most common fixed value was 0.75 (also most often used in pediatric PK studies). Although the allometric exponent remains a highly controversial topic, the use of a fixed allometric exponent of 0.75 (combined with a maturation function for younger children) was also supported by our recent study, which compared 18 approaches for scaling CL [96].

4.1.3 Size and Maturation

Using allometric models alone, which only account for size-related CL changes, is not sufficient [79, 97], particularly for neonates and infants, since CL is frequently lower than expected in these pediatric populations due to the physiological immaturity of their organs [98]. Therefore, age also needs to be taken into account, especially when analyzing data from neonates as their organ functions change very rapidly [70]. Taking both size and age into account in model development can help capture CL changes across the whole pediatric age range.

There has been much heated debate about how best to account for both size and maturation in pediatric PK studies [71, 82, 99]. While we know that "all models are wrong, some are useful" [100], a wide range of different approaches can impede our ability to compare parameters between studies of the same (or similar) drugs, by creating added complexity. Importantly, using a standardized method for parameterizing size and age across studies could aid extrapolation, improve study design, and potentially allow for smaller sample sizes. In a recently published paper, we identified the various approaches taken to scaling CL, and provided a direct comparison of these methods using the same dataset for two drugs with

different routes of elimination, specifically glomerular filtration and hepatic metabolism [96]. In light of the results, and in the knowledge that weight and age are highly correlated, albeit with the correlation varying at different ages, we recommend using a combination of allometric weight scaling with a sigmoidal maturation function (Eq. 2) to describe the changes in CL due to age and weight. By adding age into the model one can estimate the deviation (especially in the younger group) from CL, predicted using only the biological prior knowledge of allometric scaling (i.e. size).

$$CL_{child} = CL_{adult} \cdot \left(\frac{WT_{child}}{70}\right)^{b} \cdot \frac{PMA^{Hill}}{PMA_{50}^{Hill} + PMA^{Hill}}, \quad (2)$$

where CL_{child} is the predicted drug CL for a studied child, CL_{adult} is the typical CL for a 70 kg adult, b is the allometric exponent that can be estimated, but fixing to 0.75 is advocated (especially if the WT range in the studied population is small), PMA is the child's postmenstrual age (usually in weeks), PMA_{50} is the PMA when CL has reached 50% mature, and Hill is the sigmoidicity/shape parameter.

Using postmenstrual age to account for preterm neonates is important, although it should be noted that additional postnatal age scaling may be needed due to physiological changes at birth regardless of gestational age [101]. Additionally, it is sometimes also necessary to add a so-called organ function, accounting for the difference in the organ function between healthy and diseased; for example, a function including serum creatinine concentration in the case of a renally excreted drug (or another suitable biomarker reflecting renal function) [8, 101].

Including a standardized parameterization for age and size in PKPD models reported in publications would enable comparison of parameters across studies of the same or similar compounds. When planning new studies, drug-, organ- or enzyme-specific maturation models can be used in the prediction of expected CL to a similar pediatric population. Such models can also be used when fitting data, and literature models may be particularly useful in this context when small age ranges are studied [101–103]. In this case, the maturation model may be fixed or introduced as a Bayesian or 'frequentist' prior. This approach to extrapolation requires further research and is likely to be limited by drug physicochemical properties.

4.2 Dose Selection in Pediatric Studies: Extrapolation and Prediction

Determining a first pediatric dose is difficult because one needs to take into account efficacy as well as safety since it would usually not be considered ethical to give a child an ineffective dose (microdosing studies excepted [104]). Ideally, a PK study in the pediatric population would be used to define a pediatric dose, but this is not always possible [82, 105]. The pediatric dose is thus usually predicted by down-extrapolating the adult dose [106]. Historically, this has been done with empirical methods: linear weight scaling or non-linear allometric weight scaling (Eq. 3) [8, 107]:

$$Dose_{child} = Dose_{adult} \cdot \left(\frac{WT_{child}}{70}\right)^{b}, \quad (3)$$

where WT_{child} is the weight of a child in kilograms. No single value of b is suitable across the whole pediatric age range [82, 106], without also accounting for maturation [108]. Scaling CL linearly with weight from adults to neonates while ignoring maturation can lead to serious adverse reactions, such as 'gray baby syndrome' [109], and kernicterus [110], which occurred after the administration of chloramphenicol and sulphonamides to infants.

Thus, now that scaling for both size and maturation is well established (as outlined above—although there may be a time lag before it is widely adopted), a more sophisticated approach can be used to account for the rapid increase in weight and the concurrent changes in organ function maturation. Instead of scaling the dose directly, we can scale PK in order to obtain pediatric PK parameter estimates and determine the dose for a child of any age or weight, without the need for arbitrary cut-off values for either covariate (as typically specified in the non-standardized formulae for scaling CL) [8]. As mentioned above, there are strong arguments to advocate that adult CL should ideally be scaled to children using a standardized approach [96]. Using a model-based approach to guide dosing in children has previously been suggested [111, 112], and efforts to develop and validate individualized dosing software are ongoing in both children [113] and adults [114]. It should be noted that caution is required when extrapolating across populations if the covariates within the target population lie outside the range included within the model development dataset as parameter–covariate relationships can change in different pediatric populations [47]. In such instances, where this caveat is unavoidable, it may be helpful to combine 'bottom-up' approaches (e.g. PBPK) and 'top-down' approaches (e.g. population PK) to first test whether the different methods produce reasonably similar results [115].

Obese children may also need to have their dose adjusted for certain agents [116], with lean body weight being suggested as the preferred body size descriptor in this population [117, 118]. Another possible size descriptor could be fat-free mass (FFM). A model for predicting FFM

from a child's weight, age, sex, and body mass index (BMI) has recently been developed [119]; however, this model only included data from children > 3 years of age, and therefore cannot be used for neonates and infants. Furthermore, BMI is unsuitable for use in neonates. More studies focusing on obese and overweight children are needed before the best body size descriptor can be defined and before concluding whether dose adjustment is clinically necessary [116, 117].

Standardized parameterization for the scaling of CL in pediatric PK models is likely to remain a topic of some controversy, but, in light of the numerous benefits it confers, we believe its importance is paramount. However, we are not suggesting that pharmacokinetic modeling analyses should employ only this method in isolation, but would instead encourage analysts to publish their results using the standardized parameterization, in addition to the results using other parameterizations that they identify as providing a good fit to the data. This will enable ongoing collation of data about the performance of this method for drugs with different physicochemical properties and distinct pharmacokinetic profiles.

4.3 Scaling of Pharmacodynamics

While much recent emphasis has been placed on scaling PK, methods for investigating maturation and scaling of pediatric PD have frequently been neglected. This might be attributed to the fact that drug effect is more difficult to measure and evaluate, especially in neonates and infants [8]. PD endpoints can vary widely depending on the disease, therefore there will never be a single, unified method for PD scaling. For example, the GABAergic inhibitory system within the central nervous system is immature in neonates compared with adults, causing benzodiazepines to paradoxically exacerbate seizures, especially in premature newborns [120, 121]. With reference to the immune system, thymic output of T cells is higher in children compared with adults, with a peak in the thymic output at approximately 1 year of age [122]. Advanced knowledge of PD maturation might be anticipated in anesthesia, where drug effect is monitored in real time. It has long been known that for inhalational anesthetics, the alveolar concentration required for 50% of patients not to react to surgical incision initially rises, then falls with age [123]. In contrast, for propofol, Peeters et al. found that the target concentration in infants is the same as in adults, and dose differences were due to PK maturation [124]. In view of the extensive differences in PD between adults, children, and neonates, a greater use of PD modeling—rather than just simple extrapolation—is needed between these populations in order to reach and verify an efficacy target equivalent to adults [125].

4.4 Model Evaluation

A model should always be evaluated before it can be used for extrapolation [126]; several internal and external validation methods can be employed for this purpose. Internal methods include diagnostic goodness-of-fit plots, such as observed values of dependent variables plotted against population and/or individual predicted values [127, 128]. The distribution of the residual errors should also be examined to confirm whether they are normally distributed; conditional weighted residual errors can be plotted versus time or versus the population predictions to test this assumption. In addition to prediction-based evaluation, methods can also be (Monte Carlo) simulation-based, including, for example, visual predictive checks (VPCs), and plots investigating whether the distribution of normalized prediction discrepancies (NPD) follows a normal distribution [128]. Superior to internal evaluation is external evaluation, where the ability of a model to predict data that were not used for model building is assessed. When a separate dataset for external evaluation is not available, a so-called cross-validation approach can be used instead, where a dataset is split several times into a model building and model evaluation dataset, and then, for example, prediction errors are calculated [126].

5 Role of PKPD Modeling in Pediatric Trial Design

PKPD modeling can be applied to various further aspects of study design. For example, as briefly introduced above, it can be used in the context of optimal design to identify the most informative sampling schedule, number of samples per participant, and sample size; specialist software is available to support these processes [129–132]. Optimal design methods and concepts applied to pediatric PKPD studies have recently been reviewed by Roberts et al. [133]. When designing PKPD trials it is essential to account for patient acceptability and logistical factors in running the trial. Simple designs may be preferable, where feasible, providing they are scientifically sound [134], although caution should be exercised when employing opportunistic sampling to ensure methodological suitability for the drugs/analytes being studied [135, 136]. PKPD modeling can also incorporate knowledge regarding the expected placebo effect (where relevant) and anticipated rates of study attrition [137, 138]. Early engagement with children and families (patient–public involvement) to help guide decision making can provide valuable input to guide study design and research ethics committees (Institutional Review Boards) when reviewing protocols [139]. These considerations are particularly important in certain settings,

such as pediatric/neonatal intensive care, oncology, or resource-limited environments, and the relevant context-specific, ethical, and practical issues should be factored into study design [140–143].

6 Role of PKPD Modeling in Dose Optimization Strategies

Once drugs are in routine clinical use in pediatric patients, there are further applications of PKPD modeling, which have also been developing rapidly in recent years. As mentioned above, model-based decision support strategies can be used to guide TDM or dose individualization approaches in patient populations where pharmacokinetic variability is clinically important [101, 114, 144–150]. At present, the availability of the necessary software and expertise is highly variable, even in resource-rich settings, but it is anticipated that these techniques will be more frequently used in the clinic over the next 5–10 years. Should adaptive licensing become commonplace in future [103, 151, 152], then the importance of these dose optimization concepts will be further reinforced.

7 Moving Forward in this Field

The importance of PKPD modeling in pediatric drug development continues to grow, and it will clearly have a pivotal role in clinical pharmacology research throughout the lifecycle of medicinal products in the twenty-first century. Ensuring relevant stakeholders in drug development are familiar with the central tenets in PKPD modeling will enhance successful applications of these methods to improve efficiency in the drug development pipeline.

The scaling principles discussed in this review are equally applicable to small molecules and biologics [153]. Initiatives to aid data and model warehousing, such as the Drug Disease Model Resources (DDMoRe) collaboration [154, 155], and standardization of trial conduct, reporting and analysis methods [156–158], will hopefully lead to greater potential for learning across compounds.

Growing recognition that personalized medicine incorporates all aspects of variability (including genetics) will see expanding use of model-based TDM. There is also a clear need to engage with the gene therapy clinical trials community because the mathematics and statistics of dosing regimen design, and assessing treatment impact on disease progression, which have developed in clinical pharmacology, are also highly relevant in this context.

8 Conclusions

PKPD modeling will remain critically important in the design and conduct of clinical pharmacology research in children, particularly during drug development. Pediatric PK has now moved on from the paradigm 'children are not small adults' towards recognition of how important parameters scale with both size and age. Once appropriate functions for size and age are added to a PK model, this allows their effects to be delineated from other patient-specific factors such as severity of disease state and organ dysfunction. Instead of using complicated methods for scaling, which risks delivering parameters that are difficult to interpret, we advocate one standard approach for pediatric scaling of CL using a combination of allometric weight scaling to account for size-related changes in CL, and a sigmoid function to describe age-related maturation of CL. When parameterization for age and size is standardized, comparison of parameters across studies of the same or similar compounds is readily enabled. Due to the heterogeneity of PD endpoints and regulatory guidance allowing PK-only extrapolation in some cases, much less attention has been paid to the scaling and maturation of drug effects to date. Since PD endpoints are often easier to collect than PK [152, 159], it is now time that the assumptions of equal efficacy with similar exposure are challenged in all age groups using PKPD modeling in order to progress towards the ultimate goal of truly optimized pediatric pharmacotherapy.

References

1. Shirkey H. Editorial comment: therapeutic orphans. J Pediatr. 1968;72:119–20.
2. Done AK, Cohen SN, Strebel L. Pediatric clinical pharmacology and the "therapeutic orphan". Annu Rev Pharmacol Toxicol. 1977;17:561–73.
3. Christensen ML, Chesney RW. Has the 'therapeutic orphan' finally been adopted? J Pediatr Pharmacol Ther. 2003;8(3):175–6.
4. Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: the impact of evolving regulations. Adv Drug Deliv Rev. 2014;73:2–13.
5. Kimko H, Pinheiro J. Model-based clinical drug development in the past, present and future: a commentary. Br J Clin Pharmacol. 2015;79(1):108–16.
6. Manolis E, Pons G. Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. Br J Clin Pharmacol. 2009;68(4):493–501.
7. Manolis E, Osman TE, Herold R, Koenig F, Tomasi P, Vamvakas S, et al. Role of modeling and simulation in pediatric investigation plans. Paediatr Anaesth. 2011;21(3):214–21.
8. Anderson BJ, Holford NH. Understanding dosing: children are small adults, neonates are immature children. Arch Dis Child. 2013;98(9):737–44.
9. Gillis J, Loughlan P. Not just small adults: the metaphors of paediatrics. Arch Dis Child. 2007;92(11):946–7.
10. US Food and Drug Administration. Significant dates in U.S. food and drug law history. https://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm. Accessed 26 Nov 2017.
11. Kimland E, Odlind V. Off-label drug use in pediatric patients. Clin Pharmacol Ther. 2012;91(5):796–801.
12. Bellis JR, Kirkham JJ, Nunn AJ, Pirmohamed M. Adverse drug reactions and off-label and unlicensed medicines in children: a prospective cohort study of unplanned admissions to a paediatric hospital. Br J Clin Pharmacol. 2014;77(3):545–53.
13. Conroy S. Association between licence status and medication errors. Arch Dis Child. 2011;96(3):305–6.
14. Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. Expert Opin Drug Saf. 2006;5(5):703–18.
15. Safe and effective medicines for children. Washington (DC): National Academies Press; 2012.
16. Hawcutt DB, Smyth RL. The new European regulation on pediatric medicines: regulatory perspective. Paediatr Drugs. 2008;10(3):143–6.
17. Tett SE, Holford NHG, McLachlan AJ. Population pharmacokinetics and pharmacodynamics: an underutilized resource. Drug Inf J. 1998;32(3):693–710.
18. Pfister M, D'Argenio DZ. The emerging scientific discipline of pharmacometrics. J Clin Pharmacol. 2010;50(9 Suppl):6S.
19. Barrett JS, Fossler MJ, Cadieu KD, Gastonguay MR. Pharmacometrics: a multidisciplinary field to facilitate critical thinking in drug development and translational research settings. J Clin Pharmacol. 2008;48(5):632–49.
20. Zhao W, Leroux S, Jacqz-Aigrain E. Dosage individualization in children: integration of pharmacometrics in clinical practice. World J Pediatr. 2014;10(3):197–203.
21. Peck CC. Quantitative clinical pharmacology is transforming drug regulation. J Pharmacokinet Pharmacodyn. 2010;37(6):617–28.
22. Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. Annu Rev Pharmacol Toxicol. 2011;51:45–73.
23. De Cock RF, Piana C, Krekels EH, Danhof M, Allegaert K, Knibbe CA. The role of population PK–PD modelling in paediatric clinical research. Eur J Clin Pharmacol. 2011;67(Suppl 1):5–16.
24. Leil TA, Bertz RJ. Quantitative systems pharmacology can reduce attrition and improve productivity in pharmaceutical research and development. Front Pharmacol. 2014;5:247.
25. FDA's Office of Pediatric Therapeutics PMHS, and Office of Clinical Pharmacology. Modeling, simulation being used in development of pediatric drugs. AAP News. http://aapnews.aappublications.org/content/34/4/9.2.extract#. Accessed 7 Nov 2017.
26. van der Graaf PH. Regulatory modeling and simulation moves into the next gear in Europe. CPT Pharmacomet Syst Pharmacol. 2013;2:e32.
27. Sorger PK, Allerheiligen SR, Abernethy DR, Altman RB, Brouwer KL, Califano A, et al. Quantitative and systems pharmacology in the post-genomic era: new approaches to discovering drugs and understanding therapeutic mechanisms. In: An NIH white paper by the QSP workshop group; 2011. p. 1–48.
28. Minocha M, Shukla S, Gobburu J. Integration of pharmacogenomics and pharmacometrics to support drug development, regulatory and therapeutic decisions. Curr Pharmacogenom Personalized Med (formerly Curr Pharmacogenom). 2014;12(1):32–42.
29. Vinks AA, Emoto C, Fukuda T. Modeling and simulation in pediatric drug therapy: application of pharmacometrics to define the right dose for children. Clin Pharmacol Ther. 2015;98(3):298–308.
30. European Medicines Agency (EMA). Concept paper on extrapolation of efficacy and safety in medicine development. 19 March 2013. EMA/129698/2012. Human medicines development and evaluation. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/04/WC500142358.pdf. Accessed 7 Nov 2017.
31. Rodieux F, Wilbaux M, van den Anker JN, Pfister M. Effect of kidney function on drug kinetics and dosing in neonates, infants, and children. Clin Pharmacokinet. 2015;54(12):1183–204.
32. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. Clin Microbiol Rev. 2010;23(3):590–615.
33. Quijano Ruiz B, Desfontaine E, Arenas-Lopez S, Wang S. Pediatric formulation issues identified in paediatric investigation plans. Expert Rev Clin Pharmacol. 2014;7(1):25–30.
34. Nellis G, Metsvaht T, Varendi H, Toompere K, Lass J, Mesek I, et al. Potentially harmful excipients in neonatal medicines: a pan-European observational study. Arch Dis Child. 2015;100(7):694–9.
35. Turner MA, Duncan JC, Shah U, Metsvaht T, Varendi H, Nellis G, et al. Risk assessment of neonatal excipient exposure: lessons

from food safety and other areas. Adv Drug Deliv Rev. 2014;73:89–101.

36. Cram A, Breitkreutz J, Desset-Brethes S, Nunn T, Tuleu C. Challenges of developing palatable oral paediatric formulations. Int J Pharm. 2009;365(1–2):1–3.

37. Lin D, Seabrook JA, Matsui DM, King SM, Rieder MJ, Finkelstein Y. Palatability, adherence and prescribing patterns of antiretroviral drugs for children with human immunodeficiency virus infection in Canada. Pharmacoepidemiol Drug Saf. 2011;20(12):1246–52.

38. Piana C. Adherence to antiretroviral combination therapy in children: what a difference half a day makes. 2013. Doctoral thesis, Leiden University. http://hdl.handle.net/1887/22077. Accessed 7 Nov 2017.

39. Hampson LV, Herold R, Posch M, Saperia J, Whitehead A. Bridging the gap: a review of dose investigations in paediatric investigation plans. Br J Clin Pharmacol. 2014;78(4):898–907.

40. Harnisch L, Shepard T, Pons G, Della Pasqua O. Modeling and simulation as a tool to bridge efficacy and safety data in special populations. CPT Pharmacomet Syst Pharmacol. 2013;2:e28.

41. Food and Drug Administration (FDA). Guidance for industry: exposure–response relationships: study design, data analysis, and regulatory applications. Washington, DC. 2003. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM072109.pdf. Accessed 7 Nov 2017.

42. Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, Filie JD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics. 2011;128(5):e1242–9.

43. Barker CIS, Germovsek E, Hoare RL, Lestner JM, Lewis J, Standing JF. Pharmacokinetic/pharmacodynamic modelling approaches in paediatric infectious diseases and immunology. Adv Drug Deliv Rev. 2014;73:127–39.

44. Germovsek E, Barker CI, Sharland M. What do I need to know about aminoglycoside antibiotics? Arch Dis Child Educ Pract Ed. 2016;102(2):89–93.

45. Adatia I, Haworth SG, Wegner M, Barst RJ, Ivy D, Stenmark KR, et al. Clinical trials in neonates and children: report of the pulmonary hypertension academic research consortium pediatric advisory committee. Pulm Circ. 2013;3(1):252–66.

46. Leil TA, 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. 2013;47(5):557–65.

47. Cella M, Zhao W, Jacqz-Aigrain E, Burger D, Danhof M, Della Pasqua O. Paediatric drug development: are population models predictive of pharmacokinetics across paediatric populations? Br J Clin Pharmacol. 2011;72(3):454–64.

48. Cella M, Knibbe C, de Wildt SN, Van Gerven J, Danhof M, Della Pasqua O. Scaling of pharmacokinetics across paediatric populations: the lack of interpolative power of allometric models. Br J Clin Pharmacol. 2012;74(3):525–35.

49. Samant TS, Mangal N, Lukacova V, Schmidt S. Quantitative clinical pharmacology for size and age scaling in pediatric drug development: a systematic review. J Clin Pharmacol. 2015;55(11):1207–17.

50. Ramos-Martin V, Johnson A, Livermore J, McEntee L, Goodwin J, Whalley S, et al. Pharmacodynamics of vancomycin for CoNS infection: experimental basis for optimal use of vancomycin in neonates. J Antimicrob Chemother. 2016;71(4):992–1002.

51. European Medicines Agency (EMA). Reflection paper on the use of extrapolation in the development of medicines for paediatrics. 2017. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/10/WC500236640.pdf. Accessed 11 Mar 2018.

52. International Council on Harmonisation (ICH). ICH harmonised guideline. Addendum to ICH E11: Clinical investigation of medicinal products in the pediatric population E11 (R1). 2017. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/E11-R1EWG_Step4_Addendum_2017_0818.pdf. Accessed 11 Mar 2018.

53. Barker CI, Standing JF, Turner MA, McElnay JC, Sharland M. Antibiotic dosing in children in Europe: can we grade the evidence from pharmacokinetic/pharmacodynamic studies—and when is enough data enough? Curr Opin Infect Dis. 2012;25(3):235–42.

54. European Medicines Agency. Notes for guidance on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf. Accessed 7 Nov 2017.

55. European Medicines Agency. Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. Doc. Ref. EMEA/CHMP/EWP/147013/2004. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003066.pdf. Accessed 7 Nov 2017.

56. European Medicines Agency. Guideline on the investigation of medicinal products in the term and preterm neonate. 2007. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003754.pdf. Accessed 7 Nov 2017.

57. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). General clinical pharmacology considerations for pediatric studies for drugs and biological products; draft guidance for industry. 2014. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885.pdf. Accessed 7 Nov 2017.

58. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). Draft guidance for industry on pediatric study plans: content of and process for submitting initial pediatric study plans and amended pediatric study plans. 2013. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf. Accessed 7 Nov 2017.

59. Tam VH, Kabbara S, Yeh RF, Leary RH. Impact of sample size on the performance of multiple-model pharmacokinetic simulations. Antimicrob Agents Chemother. 2006;50(11):3950–2.

60. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. Br J Clin Pharmacol. 2015;79(3):357–69.

61. Turner MA. Clinical trials of medicines in neonates: the influence of ethical and practical issues on design and conduct. Br J Clin Pharmacol. 2015;79(3):370–8.

62. Wang Y, Jadhav PR, Lala M, Gobburu JV. Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies. J Clin Pharmacol. 2012;52(10):1601–6.

63. Stockmann C, Barrett JS, Roberts JK, Sherwin CMT. Use of modeling and simulation in the design and conduct of pediatric clinical trials and the optimization of individualized dosing regimens. CPT Pharmacomet Syst Pharmacol. 2015;4(11):630–40.

64. Strömberg EA, Hooker AC. Simulated model based adaptive optimal design of adult to children bridging study using FDA stopping criteria. 24th PAGE meeting, Abstr 3614. Crete, Greece; 2015. www.page-meeting.org/?abstract=3614.

65. Duffull S, Waterhouse T, Eccleston J. Some considerations on the design of population pharmacokinetic studies. J Pharmacokinet Pharmacodyn. 2005;32(3–4):441–57.

66. Kauffman RE, Kearns GL. Pharmacokinetic studies in paediatric patients. Clinical and ethical considerations. Clin Pharmacokinet. 1992;23(1):10–29.

67. Ette EI, Williams PJ. Population pharmacokinetics II: estimation methods. Ann Pharmacother. 2004;38(11):1907–15.

68. Leroux S, Turner MA, Guellec CB, Hill H, van den Anker JN, Kearns GL, et al. Pharmacokinetic studies in neonates: the utility of an opportunistic sampling design. Clin Pharmacokinet. 2015;54(12):1273–85.

69. Brouwer KL, Aleksunes LM, Brandys B, Giacoia GP, Knipp G, Lukacova V, et al. Human ontogeny of drug transporters: review and recommendations of the Pediatric Transporter Working Group. Clin Pharmacol Ther. 2015;98(3):266–87.

70. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349(12):1157–67.

71. Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. J Pharmaceut Sci. 2013;102(9):2941–52.

72. Danhof M. Systems pharmacology: towards the modeling of network interactions. Eur J Pharmaceut Sci. 2016;94:4–14.

73. US Food and Drug Administration (FDA). Pediatric trial design and modeling: moving into the next decade. Public workshop. 2017. https://www.fda.gov/Drugs/NewsEvents/ucm564111.htm. Accessed 7 Mar 2018.

74. Espie P, Tytgat D, Sargentini-Maier ML, Poggesi I, Watelet JB. Physiologically based pharmacokinetics (PBPK). Drug Metab Rev. 2009;41(3):391–407.

75. Jones HM, Mayawala K, Poulin P. Dose selection based on physiologically based pharmacokinetic (PBPK) approaches. AAPS J. 2013;15(2):377–87.

76. Edginton AN. Knowledge-driven approaches for the guidance of first-in-children dosing. Paediatr Anaesth. 2011;21(3):206–13.

77. Jamei M. Recent advances in development and application of physiologically-based pharmacokinetic (PBPK) models: a transition from academic curiosity to regulatory acceptance. Curr Pharmacol Rep. 2016;2:161–9.

78. Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. Clin Pharmacokinet. 2006;45(9):931–56.

79. Edginton AN, Willmann S. Physiology-based versus allometric scaling of clearance in children; an eliminating process based comparison. Paediatr Perinat Drug Ther. 2006;7(3):146–53.

80. Barrett JS, Della Casa Alberighi O, Laer S, Meibohm B. Physiologically based pharmacokinetic (PBPK) modeling in children. Clin Pharmacol Ther. 2012;92(1):40–9.

81. Maharaj AR, Edginton AN. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. CPT Pharmacomet Syst Pharmacol. 2014;3(11):1–13.

82. Mahmood I. Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in paediatric drug development and clinical settings. Clin Pharmacokinet. 2014;53(4):327–46.

83. Langdon G, Gueorguieva I, Aarons L, Karlsson M. Linking preclinical and clinical whole-body physiologically based pharmacokinetic models with prior distributions in NONMEM. Eur J Clin Pharmacol. 2007;63(5):485–98.

84. Sadiq MW, Nielsen EI, Karlsson MO, Friberg LE. A whole-body physiologically based pharmacokinetic (WBPBPK) model of ciprofloxacin for prediction of bacterial killing at the site of infection. 24th PAGE meeting, Abstr 3563. Crete, Greece; 2015. www.page-meeting.org/?abstract=3563.

85. Maharaj AR, Barrett JS, Edginton AN. A workflow example of PBPK modeling to support pediatric research and development: case study with lorazepam. AAPS J. 2013;15(2):455–64.

86. Sager JE, 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. 2015;43(11):1823–37.

87. Nicolas JM, Bouzom F, Hugues C, Ungell AL. Oral drug absorption in pediatrics: the intestinal wall, its developmental changes and current tools for predictions. Biopharm Drug Dispos. 2017;38(3):209–30.

88. Crawford JD, Terry ME, Rourke GM. Simplification of drug dosage calculation by application of the surface area principle. Pediatrics. 1950;5(5):783–90.

89. Holford NH. A size standard for pharmacokinetics. Clin Pharmacokinet. 1996;30(5):329–32.

90. Benedict FG. Vital energetics: a study in comparative basal metabolism. Washington: Carnegie Institution; 1938.

91. Kleiber M. Body size and metabolism. Hilgardia. 1932;6(11):315–53.

92. Kleiber M. Body size and metabolic rate. Physiol Rev. 1947;27(4):511–41.

93. Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009;24(1):67–76.

94. Johnson TN, Tucker GT, Tanner MS, Rostami-Hodjegan A. Changes in liver volume from birth to adulthood: a meta-analysis. Liver Transplant. 2005;11(12):1481–93.

95. McLeay SC, Morrish GA, Kirkpatrick CM, Green B. The relationship between drug clearance and body size: systematic review and meta-analysis of the literature published from 2000 to 2007. Clin Pharmacokinet. 2012;51(5):319–30.

96. Germovsek E, Barker CI, Sharland M, Standing JF. Scaling clearance in paediatric pharmacokinetics: all models are wrong, which are useful? Br J Clin Pharmacol. 2017;83(4):777–90.

97. Gilman JT. Therapeutic drug monitoring in the neonate and paediatric age group. Problems and clinical pharmacokinetic implications. Clin Pharmacokinet. 1990;19(1):1–10.

98. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: part I. Clin Pharmacokinet. 2002;41(12):959–98.

99. Mahmood I. Mechanistic versus allometric models for the prediction of drug clearance in neonates (< 3 months of age). J Clin Pharmacol. 2015;55(6):718–20.

100. Box GEP, Tiao GC. The collected works of George E.P. Box, vol. 1. Pacific Grove: Wadsworth Advanced Books & Software; 1985.

101. Germovsek E, Kent A, Metsvaht T, Lutsar I, Klein N, Turner MA, et al. Development and evaluation of a gentamicin pharmacokinetic model that facilitates opportunistic gentamicin therapeutic drug monitoring in neonates and infants. Antimicrob Agents Chemother. 2016;60(8):4869–77.

102. Padari H, Metsvaht T, Korgvee LT, Germovsek E, Ilmoja ML, Kipper K, et al. Short versus long infusion of meropenem in very-low-birth-weight neonates. Antimicrob Agents Chemother. 2012;56(9):4760–4.

103. Standing JF, Nika A, Tsagris V, Kapetanakis I, Maltezou HC, Kafetzis DA, et al. Oseltamivir pharmacokinetics and clinical experience in neonates and infants during an outbreak of H1N1 influenza A virus infection in a neonatal intensive care unit. Antimicrob Agents Chemother. 2012;56(7):3833–40.

104. Turner MA, Mooij MG, Vaes WH, Windhorst AD, Hendrikse NH, Knibbe CA, et al. Pediatric microdose and microtracer studies using 14C in Europe. Clin Pharmacol Ther. 2015;98(3):234–7.

105. Mahmood I. Evaluation of sigmoidal maturation and allometric models: prediction of propofol clearance in neonates and infants. Am J Ther. 2013;20(1):21–8.

106. Johnson TN. The problems in scaling adult drug doses to children. Arch Dis Child. 2008;93(3):207–11.

107. Cella M, Knibbe C, Danhof M, Della Pasqua O. What is the right dose for children? Br J Clin Pharmacol. 2010;70(4):597–603.

108. Bartelink IH, Rademaker CM, Schobben AF, van den Anker JN. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. Clin Pharmacokinet. 2006;45(11):1077–97.

109. Weiss CF, Glazko AJ, Weston JK. Chloramphenicol in the newborn infant. A physiologic explanation of its toxicity when given in excessive doses. N Engl J Med. 1960;262:787–94.

110. Silverman WA, Andersen DH, Blanc WA, Crozier DN. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. Pediatrics. 1956;18(4):614–25.

111. Kadam RS, Van Den Anker JN. Pediatric clinical pharmacology of voriconazole: role of pharmacokinetic/pharmacodynamic modeling in pharmacotherapy. Clin Pharmacokinet. 2016;55(9):1031–43.

112. Knibbe CA, Danhof M. Individualized dosing regimens in children based on population PKPD modelling: are we ready for it? Int J Pharm. 2011;415(1–2):9–14.

113. Wicha SG, Kees MG, Solms A, Minichmayr IK, Kratzer A, Kloft C. TDMx: a novel web-based open-access support tool for optimising antimicrobial dosing regimens in clinical routine. Int J Antimicrob Agents. 2015;45(4):442–4.

114. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014;14(6):498–509.

115. Feng S, Shi J, Parrott N, Hu P, Weber C, Martin-Facklam M, et al. Combining 'bottom-up' and 'top-down' methods to assess ethnic difference in clearance: bitopertin as an example. Clin Pharmacokinet. 2016;55(7):823–32.

116. Mulla H, Johnson TN. Dosing dilemmas in obese children. Arch Dis Child Educ Pract Ed. 2010;95(4):112–7.

117. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol. 2004;58(2):119–33.

118. Eleveld DJ, Proost JH, Absalom AR, Struys MM. Obesity and allometric scaling of pharmacokinetics. Clin Pharmacokinet. 2011;50(11):751–3 (discussion 5–6).

119. Al-Sallami HS, Goulding A, Grant A, Taylor R, Holford N, Duffull SB. Prediction of fat-free mass in children. Clin Pharmacokinet. 2015;54(11):1169–78.

120. Briggs SW, Galanopoulou AS. Altered GABA signaling in early life epilepsies. Neural Plast. 2011;2011:527605.

121. Montenegro MA, Guerreiro MM, Caldas JPS, Moura-Ribeiro MVL, Guerreiro CAM. Epileptic manifestations induced by midazolam in the neonatal period. Arq Neuro-Psiquiatr. 2001;59(2A):242–3.

122. Bains I, Thiebaut R, Yates AJ, Callard R. Quantifying thymic export: combining models of naive T cell proliferation and TCR excision circle dynamics gives an explicit measure of thymic output. J Immunol. 2009;183(7):4329–36.

123. Lerman J. Pharmacology of inhalational anaesthetics in infants and children. Pediatrx Anesth. 1992;2(3):191–203.

124. Peeters MY, Prins SA, Knibbe CA, DeJongh J, van Schaik RH, van Dijk M, et al. Propofol pharmacokinetics and pharmacodynamics for depth of sedation in nonventilated infants after major craniofacial surgery. Anesthesiology. 2006;104(3):466–74.

125. Kelly LE, Sinha Y, Barker CIS, Standing JF, Offringa M. Useful pharmacodynamic endpoints in children: selection, measurement, and next steps. Pediatr Res. 2018. https://doi.org/10.1038/pr.2018.38.

126. Karlsson MO, Savic RM. Diagnosing model diagnostics. Clin Pharmacol Ther. 2007;82(1):17–20.

127. Ette EI, Williams PJ, Lane JR. Population pharmacokinetics III: design, analysis, and application of population pharmacokinetic Studies. Ann Pharmacother. 2004;38(12):2136–44.

128. Nguyen TH, Mouksassi MS, Holford N, Al-Huniti N, Freedman I, Hooker AC, et al. Model evaluation of continuous data pharmacometric models: metrics and graphics. CPT Pharmacomet Syst Pharmacol. 2017;6(2):87–109.

129. Aarons L, Ogungbenro K. Optimal design of pharmacokinetic studies. Basic Clin Pharmacol Toxicol. 2010;106(3):250–5.

130. Hooker A, Vicini P. Simultaneous population optimal design for pharmacokinetic–pharmacodynamic experiments. AAPS J. 2005;7(4):E759–85.

131. Nyberg J, Bazzoli C, Ogungbenro K, Aliev A, Leonov S, Duffull S, et al. Methods and software tools for design evaluation in population pharmacokinetics–pharmacodynamics studies. Br J Clin Pharmacol. 2015;79(1):6–17.

132. Nyberg J, Karlsson MO, Hooker AC. Simultaneous optimal experimental design on dose and sample times. J Pharmacokinet Pharmacodyn. 2009;36(2):125–45.

133. Roberts JK, Stockmann C, Balch A, Yu T, Ward RM, Spigarelli MG, et al. Optimal design in pediatric pharmacokinetic and pharmacodynamic clinical studies. Paediatr Anaesth. 2015;25(3):222–30.

134. Thomson AH, Elliott HL. Designing simple PK–PD studies in children. Paediatr Anaesth. 2011;21(3):190–6.

135. Kipper K, Barker CIS, Standing JF, Sharland M, Johnston A. Development of a novel multipenicillin assay and assessment of the impact of analyte degradation: lessons for scavenged sampling in antimicrobial pharmacokinetic study design. Antimicrob Agents Chemother. 2018;62(1):e01540–617.

136. Standing JF, Anderson BJ, Holford NH, Lutsar I, Metsvaht T. Comment on pharmacokinetic studies in neonates: the utility of an opportunistic sampling design. Clin Pharmacokinet. 2015;54(12):1287–8.

137. Anderson BJ, Hannam JA. Considerations when using pharmacokinetic/pharmacodynamic modeling to determine the effectiveness of simple analgesics in children. Expert Opin Drug Metab Toxicol. 2015;11(9):1393–408.

138. Knebel W, Rogers J, Polhamus D, Ermer J, Gastonguay MR. Modeling and simulation of the exposure–response and dropout pattern of guanfacine extended-release in pediatric patients with ADHD. J Pharmacokinet Pharmacodyn. 2015;42(1):45–65.

139. Modi N, Vohra J, Preston J, Elliott C, Van't Hoff W, Coad J, et al. Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees. Arch Dis Child. 2014;99(10):887–91.

140. Kleiber N, Tromp K, Mooij MG, van de Vathorst S, Tibboel D, de Wildt SN. Ethics of drug research in the pediatric intensive care unit. Paediatr Drugs. 2015;17(1):43–53.

141. Ward RM, Sherwin CM. Ethics of drug studies in the newborn. Paediatr Drugs. 2015;17(1):37–42.

142. MacLeod SM, Knoppert DC, Stanton-Jean M, Avard D. Pediatric clinical drug trials in low-income countries: key ethical issues. Paediatr Drugs. 2015;17(1):83–90.

143. Schechter T, Grant R. The complexity of consenting to clinical research in phase I pediatric cancer studies. Paediatr Drugs. 2015;17(1):77–81.

144. Barrett JS. Paediatric models in motion: requirements for model-based decision support at the bedside. Br J Clin Pharmacol. 2015;79(1):85–96.

145. Valitalo PA, van den Anker JN, Allegaert K, de Cock RF, de Hoog M, Simons SH, et al. Novel model-based dosing guidelines for gentamicin and tobramycin in preterm and term neonates. J Antimicrob Chemother. 2015;70(7):2074–7.

146. Jelliffe RW. Some comments and suggestions concerning population pharmacokinetic modeling, especially of digoxin, and its relation to clinical therapy. Ther Drug Monit. 2012;34(4): 368–77.

147. Neely M, Margol A, Fu X, van Guilder M, Bayard D, Schumitzky A, et al. Achieving target voriconazole concentrations more accurately in children and adolescents. Antimicrob Agents Chemother. 2015;59(6):3090–7.

148. Rao A, Standing J, Naik S, Savage M, Sanderson I. Mathematical modelling to restore circulating IGF-1 concentrations in children with Crohn's disease-induced growth failure: a pharmacokinetic study. BMJ Open. 2013;3(5):e002737.

149. Hennig S, Nyberg J, Fanta S, Backman JT, Hoppu K, Hooker AC, et al. Application of the optimal design approach to improve a pretransplant drug dose finding design for ciclosporin. J Clin Pharmacol. 2012;52(3):347–60.

150. Hennig S, Holthouse F, Staatz CE. Comparing dosage adjustment methods for once-daily tobramycin in paediatric and adolescent patients with cystic fibrosis. Clin Pharmacokinet. 2015;54(4):409–21.

151. Eichler HG, Oye K, Baird LG, Abadie E, Brown J, Drum CL, et al. Adaptive licensing: taking the next step in the evolution of drug approval. Clin Pharmacol Ther. 2012;91(3):426–37.

152. Johansson AM, Hill N, Perisoglou M, Whelan J, Karlsson MO, Standing JF. A population pharmacokinetic/pharmacodynamic model of methotrexate and mucositis scores in osteosarcoma. Ther Drug Monit. 2011;33(6):711–8.

153. Robbie GJ, Zhao L, Mondick J, Losonsky G, Roskos LK. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. Antimicrob Agents Chemother. 2012;56(9):4927–36.

154. Drug Disease Model Resources Consortium. DDMoRe website. http://www.ddmore.eu/. Accessed 26 Nov 2017.

155. Harnisch L, Matthews I, Chard J, Karlsson MO. Drug and disease model resources: a consortium to create standards and tools to enhance model-based drug development. CPT Pharmacomet Syst Pharmacol. 2013;2:e34.

156. Klassen TP, Hartling L, Hamm M, van der Lee JH, Ursum J, Offringa M. StaR Child Health: an initiative for RCTs in children. Lancet. 2009;374(9698):1310–2.

157. Wittmeier KD, Craig J, Klassen TP, Offringa M. The mission of StaR Child Health is to improve the quality of the design, conduct, and reporting of pediatric clinical research by promoting the use of modern research standards. Introduction. Pediatrics. 2012;129(Suppl 3):S111.

158. Van't Hoff W, Offringa M. StaR Child Health: developing evidence-based guidance for the design, conduct and reporting of paediatric trials. Arch Dis Child. 2015;100(2):189–92.

159. Standing JF, Hammer GB, Sam WJ, Drover DR. Pharmacokinetic–pharmacodynamic modeling of the hypotensive effect of remifentanil in infants undergoing cranioplasty. Paediatr Anaesth. 2010;20(1):7–18.

160. National Institute of Child Health and Human Development. About the BPCA: background of the best pharmaceuticals for children act (BPCA). https://bpca.nichd.nih.gov/Pages/default.aspx. Accessed 7 Nov 2017.

161. Ward RM, Kauffman R. Future of pediatric therapeutics: reauthorization of BPCA and PREA. Clin Pharmacol Ther. 2007;81(4):477–9.

162. US Food and Drug Administration. Regulatory information. Fact sheet: pediatric provisions in the Food and Drug Administration Safety and Innovation Act (FDASIA). https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm311038.htm. Accessed 7 Nov 2017.