Dokoumetzidis Aristides (Orcid ID: 0000-0001-5087-4003)
Knibbe Catherijne AJ (Orcid ID: 0000-0001-9893-4415)
De wildt Saskia (Orcid ID: 0000-0002-0502-0647)
Foissac Frantz (Orcid ID: 0000-0002-9928-3404)
Zhao Wei (Orcid ID: 0000-0002-1830-338X)
Standing Joseph F (Orcid ID: 0000-0002-4561-7173)
Tréluyer Jean-Marc (Orcid ID: 0000-0002-2045-4742)

General clinical and methodological considerations on the extrapolation of pharmacokinetics and optimisation of study protocols for small molecules and monoclonal antibodies in children

Authors:

Naïm BOUAZZA[1,2,3], Aristides DOKOUMETZIDIS[4], Catherijne A.J. KNIBBE[5,6], Saskia N. de WILDT[7,8], Claire AMBERY[9], Pieter De COCK[10,11,12], Elke GASTHUYS[13], Frantz FOISSAC[1,2,3], Saïk URIEN[1,2,3], Anna-Karin HAMBERG[14], Italo POGGESI[15], Wei ZHAO[16,17,18], An VERMEULEN[13], Joseph F STANDING[19,20], Jean-Marc TRÉLUYER[1,2,3] *On behalf of c4c Expert group on Pharmacometrics.*

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Affiliations:

[1] Université de Paris, Pediatric and perinatal drug evaluation and pharamcology, F-75006 Paris, France ; [2] Unité de Recherche Clinique Université de Paris Necker-Cochin, AP-HP, 89 rue d'Assas, 75006, Paris, France ; [3] CIC-1419 Inserm, Cochin-Necker, 149 Rue de Sèvres, 75015, Paris, France ; [4] Department of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece ; [5] Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden University, Einsteinweg 55, 2333, CC, Leiden, The Netherlands ; [6] Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, The Netherlands ; [7] Department of Pharmacology and Toxicology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands; [8] Department of Intensive Care and Paediatric Surgery, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands ; [9] Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline plc, London, UK ; [10] Department of Basic and Applied Medical Sciences, Ghent University, Ghent, Belgium ; [11] Department of Pharmacy, Ghent University, Ghent, Belgium; [12] Department of Pediatric Intensive Care, Ghent University Hospital, Ghent, Belgium ; [13] Department of

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Bioanalysis, Faculty of Pharmaceutical Sciences, University of Ghent, Ghent, Belgium ; [14] Department of Clinical Pharmacology, Uppsala University Hospital, Uppsala, Sweden ; [15] Clinical Pharmacology & Pharmacometrics, Janssen Research & Development, Beerse, Belgium ; [16] Department of Clinical Pharmacy, Key Laboratory of Chemical Biology (Ministry of Education), School of Pharmaceutical Sciences, Cheeloo College of Medicine, Shandong University; [17] Department of Pharmacy, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jinan, China; [18] Clinical Research Centre, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Jinan, China ; [19] Infection, Inflammation and Immunology, UCL Great Ormond Street Institute of Child Health, London, UK ; [20] Department of Pharmacy, Great Ormond Street Hospital for Children, London, UK

Corresponding author

Naïm Bouazza, PhD

Université de Paris

Paediatric and perinatal drug evaluation and pharmacology

F-75006 Paris, France

E-mail : naim.bouazza@aphp.fr

Running Head: Challenges in paediatric extrapolation and trial design

Key words: modelling, simulation, paediatric, pharmacometrics, PBPK, allometry

Abstract

Pharmacometric modelling plays a key role in both the design and analysis of regulatory trials in paediatric drug development. Studies in adults provide a rich source of data to inform the paediatric investigation plans, including knowledge on drug pharmacokinetics, safety and efficacy. In children, drug disposition differs widely from birth to adolescence but extrapolating adult to paediatric pharmacokinetics, safety and efficacy either with pharmacometric or physiologically-based approaches can help design or in some cases reduce the need for clinical studies. Aspects to consider when extrapolating pharmacokinetics (PK) include, the maturation of drug metabolizing enzyme expression, glomerular filtration, drug excretory systems and the expression and activity of specific transporters in conjunction with other drug properties such as fraction unbound. Knowledge of these can be used to develop extrapolation tools such as allometric scaling plus maturation functions or physiologically based pharmacokinetics. Pharmacokinetic/pharmacodynamic (PKPD) approaches and well-designed clinical trials in children are of key importance in paediatric drug development

In this white paper, state-of-the-art of current methods used for paediatric extrapolation will be discussed. This paper is part of a c4c implementation of innovative methodologies including pharmacometric and PBPK modelling in clinical trial design/paediatric drug development through dissemination of expertise and expert advice. The suggestions arising from this white paper should define a minimum set of standards in paediatric modelling and contribute to the regulatory science.

Background

In 1994 the U.S. Food and Drug Administration (FDA) introduced the application of adult-to-children extrapolation. They proposed a framework for the extrapolation of efficacy from adults to the paediatric population that was further discussed in the General Clinical Pharmacology Considerations for Paediatric Studies published in 2014 (1). This paediatric decision tree suggests that certain steps in paediatric drug development can be skipped depending on what is already known (i.e., similarity between adults and children regarding disease etiology and exposure-response relationships, pharmacodynamic surrogate). However, pharmacokinetics still needs to be characterized in the paediatric population whatever the extrapolation framework. The European Medicines Agency (EMA) also stated the benefit of extrapolation from adults in the Extrapolation Concept Paper published in 2012 and in the reflection paper in 2018 (2). This concept paper argued the possibility to extend and refine an algorithm for extrapolation towards paediatric drug development that was based on three main topics: pharmacology, disease manifestation and progression and clinical response to treatment. The paediatric population includes children from birth to 17 years of age. This population is known to be heterogeneous in terms of age, height, body weight and maturation of physiological processes.

Population pharmacokinetics (PK) relates systemic drug concentration to the dosing regimen via compartimental model parameters that quantify distribution and elimination (3). The population approach (4), i.e nonlinear mixed effects modelling, is the gold standard for the simultaneous analysis of concentration-time data from various individuals since i) it takes into account repeated measures over time, ii) it allows the identification and estimation of different sources of variability (between-subject, between-occasion and residual variabilities) and iii) it can take into account individual characteristics of PK parameters through covariate analysis.

The major assumption here to establish the dose rationale is that the systemic exposure is a surrogate, i.e., relevant target organs and tissues are assumed to be in equilibrium with plasma concentrations.

Altogether, a final popPK model including size and age effects based on adult data allows the prediction of pharmacokinetics in children.

Body size is usually the key covariate associated with clearance and volume terms according to the allometric rule (5). It has been suggested that the size effect can be refined by estimating the respective fat-free mass and fat mass contributions, this has been shown for busulfan pharmacokinetics for example (6). Finally, if the population includes neonates and infants, a maturation function for elimination clearance should be implemented in addition to size effects. Further discussion of size-based allometric scaling and maturation functions are detailed in a specific section below.

Physiologically based pharmacokinetic modelling entails generating a PK model based on expected tissue composition and blood flows through physiological compartments informed by literature data on body physiology, and physicochemical properties of the drug in question informing partition in, and transit through, organs and tissues in the body (7). This approach uses complex models and integrates detailed biological processes while keeping a compartmental approach. It provides a physiology-informed way to predict the expected PK of drugs in the paediatric population (8) as detailed in the physiologically based pharmacokinetic section. Differences between population pharmacokinetic and physiologically based pharmacokinetic models are summarized in table 1.

Once an expectation of the PK in the paediatric population has been generated, a clinical study will need to be done to allow confirmation of the expected behavior of the drug under consideration. In general, it is often only feasible to recruit a small number of subjects in paediatric PK studies. It is therefore important to extract the highest quality information possible from each subject, whilst trying to minimise the impact on the patient (who will likely receive no benefit by donating PK samples) through reducing the number and volume of blood samples. Therefore, optimising the design of such studies is important. Setting up a PK study requires investigators to prospectively specify the study design including the number of patients, number and times of blood sampling as well as the modelling approach that will be used to analyze the data in the protocol.

The aim of this paper is to summarize the current knowledge regarding extrapolation of information from the adult to the paediatric population through pharmacokinetic extrapolation tools such as allometry, maturation functions, pharmacometrics and physiologically based pharmacokinetics. This paper is addressed to pharmaceutical companies, regulatory agencies and academicians about how to incorporate the latest knowledge regarding such pharmacokinetic extrapolation. The paper will also discuss the specificities of neonatal pharmacometric studies, where the maturation process estimation is mandatory, as well as the importance of well-designed paediatric clinical trials.

Allometric scaling and age-related maturation

Allometric scaling is a common method to extrapolate the pharmacokinetics (most importantly clearance) of a drug in humans in the absence of clinical data. The approach has also been successfully used to predict the pharmacokinetics of a drug in children when adult PK data are available (9,10). As a concept it relies on the empirical observation that metabolic rate (and hence drug clearance) scales according to body size. More generally, it derives from a property in nature related to the scaling of various biological processes and quantities such as heart rate, organ weight, blood flows, etc. with respect to size, across a wide range of sizes of orders of magnitude apart. Mathematically, allometric scaling is a function of the body weight, BW

$$P = P_{TYP} \cdot (BW/BW_{REF})^b,$$

where b is a power exponent and P is the parameter under study, the subscripts TYP and REF denote the typical parameter value corresponding to the reference BW .

The exponent b carries a physical meaning of dimensionality. There are 3 main *a priori* values for the exponent: 1, 2/3 and 3/4. The value of 1 represents a proportional relationship of the quantity to weight (isometric) and is a straightforward scaling for any extensive quantity such as drug volume of distribution. The value 2/3 relates to the body surface area, i.e., drug transport and diffusion take place through membranes and the rate is proportional to their effective surface area. In clinical pharmacology this is expressed by dosing regimens per m2 and was first suggested in 1950 (11). The value 3/4 or 0.75 (allometric) comes from metabolic rate observations from microbes to whales confirmed by mathematical theories (12–14). However, some other studies have reported values different from 0.75 (15). Figure

1 illustrates exposure-matching between adults and children according to linearity assumption between drug clearance and bodyweight or according to 3/4 allometry based assumption using a previous lamivudine popPK model in children (16).

The age of 2 years old is considered a milestone for the maturation of the activity of drug metabolizing enzymes related to PK, most importantly cytochrome P450 family enzymes supporting that children are indeed small adults(17)! This age limit includes the renal function maturation. Therefore, an estimation of the maturation function requires data from children below the age of 2 yrs. The typical maturation function relates the maturation to the post-menstrual age PMA as

$$MAT = PMA^H/(PMA^H + PMA_{50}^H)$$

where MAT varies from 0 to 1 (adult maturation) when PMA increases. The PMA_{50} is the PMA value where MAT is half the adult maturation value and the exponent H influences the shape of the curve near the PMA_{50} value. Therefore, the allometric rule can be used to describe the CL terms in this very young age group :

$$CL = CL_{TYP} \cdot (BW/BW_{REF})^{0.75} \cdot MAT$$

Otherwise, when CL is related to BW alone, different weight-based allometric exponents must be used for clearance depending on cut-off age values in neonates and infants (18).

Therefore, the extrapolation of adult pharmacokinetics is fully acceptable for children more than 5-yr old where the maturation process is achieved (MAT~1). Below 5-yr old, specific data obtained in this very young age group, especially in infants and neonates, must be available.

Related to the debate on the 0.75 exponent the EMA has taken a clear position (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers) which states that when extrapolating to children, exponents estimated from adult data should be avoided when characterizing PK in children based on relatively limited data. Instead fixing to theoritical values in addition with a function to characterize maturation in younger children should be preferred but the validity of this *a priori* assumption should be justified. On the other hand, the FDA has kept a more neutral position.

Overall, extrapolation from adults directly to the youngest children can be considered risky, because other factors than age and weight may influence maturation (see "Specificities in neonatal studies" section). A stepwise approach could be used for PK confirmation, subjects in the age range of 6-12 years, and of 2-5 years are subsequently studied, eventually semi-staggered, to confirm the dose predictions using allometry and avoid safety problems. However, studies in adolescents can be considered as inefficient, since they can be easily implemented within the clinical development of the product in the adult population. Availability of at least a subgroup of the adolescent population in a Phase III trial could form a stronger basis for extrapolation of data to younger patients. Finally, subjects from 1month to 2 years and from birth to 1-month old are studied, while the model is being updated with the new data as these become available. However, these staggered study designs have several drawbacks such as slowing down patient recruitment, therefore less conservative approaches could be considered if there is confidence on how maturation will likely play out, perhaps using data from other similar drugs. In all cases, these assumptions should be confirmed using diagnostic evaluation tools. In this regard, drug disposition should be re-evaluated within a continuum throughout age groups as well as across physiopathological conditions. This PK analysis should be able to capture all observations, which can be illustrated by plots illustrating the predictive value of the PK model based on the covariates of interest. For instance, goodness of fit plots split in quartiles for weight, age or diseases, showing similar performance of the model across these quartiles can be shown, in addition to plots showing interindividual variability in clearance or volume versus the main covariates of interest like weight, age, and/or disease status can further increase the confidence in the model for deriving subsequent dose recommendations.

Finally, for new drugs under development, in children more than 5-yr old PK parameters can be safely extraplolated from adult studies, since the maturation is achieved as discussed above. Thus blood samplings could be avoided in these children.

Besides allometric scaling plus age-maturation function for very young children, other tools such as PBPK models as well as additional preclinical information to address developmental issues could be informative, see next section. A complete extrapolation concept (EMA/189724/2018) should be built that scientifically justifies the entire exercise where even

the exposure - response relationship is addressed (and not taken for granted) and the appropriate PK parameter that best represents exposure should be justified. All decisions should be taken in light of the totality of the data.

Physiologically based pharmacokinetics

Over the years, physiologically based pharmacokinetic modelling (PBPK) has provided a (semi-) mechanistic framework to acquire insights on adult drug disposition. By integrating both drug-related and physiological parameters (obtained by in vitro, in vivo and in silico (pre)clinical studies) as well as trial-specific parameters, these models can *inter alia* inform on trial design, dosing regimens, drug-drug interactions (DDI) or drug efficacy/safety (19,20). More recently in paediatrics, PBPK modelling and simulation has emerged and served as a valuable predictive tool for a variety of applications from selection of potential drug candidates, mechanistic understanding of the maturation of ADME pathways to designing clinical trials and optimizing dosing regimens (20–22). Several groups have reported promising results by using PBPK modelling and simulation to predict the PK in paediatric patients for a variety of drug classes (8,20,22–27). The use of PBPK modelling in paediatric drug development is achieving additional critical mass since both the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA) issued draft guidelines to encourage PBPK modelling in this population (1,28).

A detailed tutorial on how to develop a paediatric PBPK model has been provided in different reviews published by Leong et al. (21), Jones and Rowland-Yeo (29), Maharaj and Edington (30), Lin et al. (31) and Verscheijden et al. (32). In brief, first an adult PBPK model needs to be developed implementing all relevant physiological system- and drug-related input parameters. Second, the adult model performance needs to be evaluated by simulating the PK and by comparing the plasma concentration-time profiles against observed adult profiles. During this evaluation, the trial design used in the simulations (i.e., sample size, PK sampling strategy) has to match the design reported in the corresponding clinical studies. Third, after establishing confidence in the performance of the adult PBPK model, physiological system-specific input parameters need to be translated to the paediatric population using prior

physiological information about growth and maturation of relevant processes and parameters. The drug-related parameters however need not to be adapted. During this process, it is important to bear in mind that paediatric PBPK models need to reflect the physiological changes that occur during development, preferably by implementing time-varying physiology into these models.

Moreover, when buiding a paediatric PBPK model from an adult one, some assumptions need to be made: 1) the same elimination pathways contribute to overall clearance, 2) the overall model structure is similar and 3) there is no impact of (paediatric) disease state on the ontogeny of any of the elimination pathways involved (20). However, some of these assumptions may not always hold or cannot always be verified due to lack of data and this issue may become more prominent as the age of the paediatric population decreases. In contrast, in case all of the different elimination pathways are known, maturation in each of the pathways involved can be used to predict changes in overall clearance with different pathways contributing to overall plasma clearance at different levels depending on age (33).

An issue in PBPK modelling that still needs resolution is the fact that maturation functions often differ from one software or source to the next, which may lead to different dose recommendation results (26). PBPK model building and evaluation will often start using the default paediatric population parameters available in the software and will be adapted accordingly to simulate and to compare to the observed (sparse) PK in children that is available. It is emphasized here that these data may also include PK data of the drug used for other indications. Using these data, the model can be fine-tuned in a stepwise fashion ultimately allowing for prediction in younger children, even infants and neonates, by applying the “learn-and-confirm” principle (Figure 2). In case no data are yet available, it has been proposed to evaluate the predictive properties of the PBPK model against compounds metabolized via the same enzymes in children, having the same extraction ratio and absorption characteristics as the drug of interest with adequate performance (34,35).

Although PBPK modelling and simulation is an emerging field in paediatric drug development, important hurdles will still have to be overcome. The advantage of using PBPK modelling over allometric scaling and other empiric scaling methods in the younger paediatric population (<6

years) is that it can implement growth and maturation to account for the ontogeny of the physiological processes that govern drug disposition (20,22). The latter is particularly applicable when performing studies in children aged < 2-5 years due to poor body-weight correlation (9,36). However, this requires a comprehensive understanding about physiological, biochemical and physicochemical processes, which is lacking, particularly in the youngest age groups including preterm neonates. Furthermore, it also requires knowledge of the drug properties (information on all elimination routes, enzymes and transporters involved, plasma protein binding to albumin/α1-acid glycoprotein, etc.) of the compound under study, which are not always available, especially when investigating older marketed drugs (37).

Special attention should be given to stimulate research on physiological mechanisms governing the (gestational) age-dependent changes in absorption, distribution, metabolism and elimination of drugs in the youngest age groups including preterm neonates, since PBPK modelling might become a useful tool in this orphaned population (38,39) while there still seems a paucity of adequate, validated data (40). Another prominent gap in paediatric PBPK modelling is that variability prediction for model parameters is rather an empirical process heavily relying on assumptions made by the respective researchers. Additional studies evaluating the parameter variability for different disease types across the paediatric population are required to better account for this variability (20,31). The unmet need for additional information on the disease-specific influence on model performance, as shown for example for midazolam (41), was also stated in different studies, whereby this missing information is needed for further model refinement (42).

Given the scarcity of good quality paediatric data, the level of confidence in paediatric PBPK predictive performance is currently rather on the low to moderate end, posing a considerable challenge in predicting the PK especially in very young children (0-5 years) and in preterm neonates in particular (19). This raises the question if PBPK modelling should always be chosen over other simpler methods such as allometry with age-dependent function, between drug-extrapolation of covariate functions for drugs eliminated by the same pathway, semi-physiological modelling. This question certainly applies when studying adolescents (12 to 16/18 years), whereby application of allometric power models almost always accurately

predict drug clearance since both renal capacity and hepatic enzyme expression have reached adult levels (43). To assist with this selection process, Calvier et al. (44) has developed a useful decision tree allowing to select the method which accurately scales clearance according to the paediatric age range and drug properties under investigation. In this work, they showed that down to paediatric ages of 5 years, PBPK does not result in more precise clearance and hence dose predictions, whatever the elimination route of the drug is. Table 2 summarizes the advantages and uncertainties of both extrapolation approach, allometry and PBPK.

In conclusion, PBPK has become increasingly established as a reliable decision-making predictive tool in paediatric drug development. However, PBPK is not always the method of choice whereby the applicability should be evaluated on a case-by-case basis. Additional extensive research is urgently required to fill the knowledge gaps and to improve PBPK performance.

Specificities in neonatal studies

In the neonates and infants, PK variability is usually large and not well predicted resulting in difficulties in dose selection. Therefore, there is a need for a quantitative and systematic approach for the dose rationale in this group of patients, at the design phase of a clinical protocol.

The hospital neonatal unit, where the vast majority of medicines prescribed to newborns are administered, is arguably the most pharmacokinetically diverse place within any healthcare setting. Patients can range in size by 10-fold (400g – 4kg) whilst eliminating organ maturation, enzyme expression and body composition vary radically over the gestational and postnatal age demographic. Particularly preterm neonates may require treatment over several months at the hospital, during which many changes occur that are of influence on a drugs optimal dose. To depict the population PK characteristics of drugs in neonates, considerations of these clearance maturation processes and potential volume of distribution differences are required, which means that adequately capturing often time varying demographic information is of great importance in ph

armacometric trials (45).

Gestational age (GA) and post-natal age (PNA) correlate with antenatal and postnatal renal maturation respectively, as well as other elimination processes, and this has led to postmenstrual age (PMA), the combination of both, GA and PNA, which is used. Hence, GA, PNA and PMA need to be considered in study design as when it comes to planning which age groups to enroll. Which of these variables best describes pharmacokinetic maturation may be both drug and disease specific, and therefore, in order to cover the entire range, it seems that recruiting a number of babies with varying GA and PNA and consequently a varying PMA is generally a reasonable strategy. However there is some additional uncertainty in extrapolation considering that maturation processes are not limited to enzymatic or renal ontogeny. It also includes immune system and organ function differences which can be altered as consequence of either disease or therapeutic interventions (such as the use of corticosteroids or surfactants in preterm newborns).

It is likely that when using PMA the true maturational relationship is sigmoidal and requires inclusion of patients from birth up to around 1 year of age to fully characterise the maturation profile shape. Ideally neonatal PK should therefore be collected with a view to a joint analysis including infants and children so that the full maturation profile can be estimated, but this is not always possible. Tang et al. (46) investigated GA, PNA, PMA and the combination of GA and PNA to outline the population pharmacokinetics of amoxicillin in neonates and young infants. They found that the combination of GA and PNA is superior to PMA alone. While Anderson et al. (47) concluded that PMA partially (18.2%) and significantly accounts for the vancomycin clearance variability in premature neonates. When large populations have been studied, a data-driven covariate modelling approach has been used (48), but another alternative is to use biological prior information by fixing in a PMA-based maturation function based on renal (49) or enzyme expression maturation (50). However, in cases where babies in the first week of life have been recruited, regardless of GA, a further PNA-based term has often been required when this approach is used (51–53). The difference in GFR between pre-term and full-term neonates with the same postmenstrual age has recently been shown to persist up to around 1.25 years, although the degree to which this difference would be large enough to require different dosing is probably limited to the very early postnatal period (54).

The recommendation on enrollment within the neonatal period is therefore to ensure that for drugs likely to be required in the first week of life, sufficient numbers of these patients are recruited, preferably with varying gestational age in case the drug is used for both preterm and term neonates. Secondly, since maturation continues beyond the neonatal period, it is less important to seek to recruit babies with every conceivable GA/PNA combination, rather to ensure a balance between early PNA and late PNA for neonates within the range of GA that is of relevance of the drug of interest. Kane et al (51) used simulation-estimation to adequately power a neonatal fosfomycin PK study, and a similar approach using published maturation functions could be used to ensure the expected target demographics would be able to capture expected PMA or GA/PNA associated maturation.

Optimal sampling times for PK characterization to minimize invasiveness

The choice of the experimental design is crucial for efficient estimation of pharmacokinetic parameters. A design in pharmacometric studies is defined by the number and specification of elementary designs along with the number of subjects. The elementary design corresponds to a group of subjects with identical design features. The design should consider a balance between the number of subjects and the number of samples per subject, as well as the allocation of informative times and doses, according to practical constraints (55).

Non-compartmental pharmacokinetic data analysis requires multiple samples (typically >10 samples per person) collected at fixed intervals from health volunteers or adult patients (56). However, such dense sampling is rarely feasible in children especially in neonates. Challenges in obtaining pharmacokinetic data in neonates lie in the difficulty to capture the number and volume of blood samples, and timely collection in the busy intensive care unit further complicates recruitment. Besides, it can be troublesome to obtain informed consent from parents for a non-therapeutic purpose such as PK sampling (57).

To optimize sampling times and minimize invasiveness, some authors have proposed the use of opportunistic samples (samples collected from blood remaining after routine laboratory tests as part of clinical care). This approach generates sparse, unbalanced datasets, and

sample timing/number of samples can vary between patients (56,58). This approach however is not recommended in regulatory trials as highlighted by the following example:

Leroux et al. (57) undertook a study with both optimally pre-determined and opportunistic sampling in a ciprofloxacin population pharmacokinetic study and compared models based on the data from opportunistic blood samples, predetermined samples and all samples. Whilst the opportunistic model was able to determine clearance and steady-state volume, because samples were taken at random rather than optimally informative times, a very different disposition model was estimated leading to huge differences in predicted Cmax between the opportunistic model and models based on optimally timed and full datasets (59). The conclusion from this work was that the sparse but optimally timed samples would have been more reliable to build a model than the random opportunistic samples, and indeed since the same parameters were estimated using only the timed or full data, the opportunistic samples did not yield any benefit.

Although a plethora of population pharmacokinetic studies of antimicrobials using opportunistic sampling have been published (46,57,60,61), results of studies using only opportunistic samples should not generally be recommended for regulatory trials unless detailed justification can be made that such sampling does not lead to biased parameter estimates. Furthermore, the ethical aspect of opportunistic sampling should also be taken into account. Since the final data structure is unknown at the outset, it is therefore uncertain whether an adequate number or timing of PK samples will be collected to generate precise PK parameter estimates with a purely opportunistic approach.

Optimal design can be used to specify the most informative sparse sampling times, and this was successfully highlighted by Germovsek et al (49) in the neoMero studies whereby ED-optimal sampling allowed for only 3 samples per child to derive precise parameter estimates. Other useful methods for determining whether a sampling design will yield precise parameter estimates exists such as FIM based methods or simulation-estimation whereby data are simulated from a proposed model under a proposed design and then checking the precision of resulting estimates (51).

Ethically, since limited blood volumes and/or number of samples can be used for PK sampling in children, it is vital that sampling schedules are designed to obtain the maximally precise PK information whilst being minimally invasive in terms of sample number and volume. It is emphasized however, that assumptions on maturation of PK parameters underlying the optimal sampling calculations play an important role in the identification of the optimal sampling times and therefore sensitivity analyses using alternative assumptions on the maturation in the PK are of relevance.

Finally, making sure the documentation of blood draw time is accurate and where possible moving dosing or sampling times to coincide with routine blood sampling visits will help to achieve this aim.

The issue that remains critical for most clinical programs is the dose rationale and recommendations that arise from the pharmacokinetic, efficacy and safety data collected in these studies. Beyond the sample size determination as discussed above, the design should point out patient stratification by weight rather than age. Also, other strategies including pooled or integrated data analysis or adaptive protocol design are likely to be useful in this context.

Dose-finding trials in children

In cases where the exposure-response relationship cannot be assumed to be the same between adults and children of all ages or in case of specific childhood disease, both FDA and EMA agree on the need of dose-finding trials followed by confirmation of dosage effectiveness in children in addition to PK study. Dune et al. (62) reviewed 370 paediatric studies submitted to the FDA between 1998 and 2008 and identified cases in which efficacy was extrapolated or not from adult data or other data. In this review, they found that no extrapolation of efficacy was performed for 17% of cases, including mainly the following therapeutic indications: major depressive disorder, asthma, and solid tumors. In most cases, efficacy was not extrapolated because the disease or condition was not considered to be sufficiently similar in the adult and paediatric populations. Other cases include products for which indication was not authorized for use in adults and efficacy could not be extrapolated.

The dose-finding trial design selected should provide the best evidence (regarding both drug safety and efficacy) while minimizing the number of patients to be included. Paediatric data are often scarce, and paediatric dose ranges that are evaluated are usually derived from existing adult dose trials (63).

Modelling approaches in this area are of great interest. The continual reassessment method (CRM) remains at present the most published in the framework of Bayesian dose-finding clinical trials (64). Alternative versions of the conventional CRM method have been proposed. Among these, one is of particular interest in the context of paediatric trials and is referenced under the name b-CRM, for bivariate-CRM (65). This method allows a sequential and joint assessment of efficacy and toxicity of the drug. This is a sequential (i.e., analysis is performed at each stage of the test) and adaptative method based on empirical or logistic parametric models linking dose to both efficacy and toxicity. Patient cohorts may consist of one or more patients depending on the design. This method re-evaluates the dose to be administered to each new cohort included in the study by re-estimating the probability of efficacy and toxicity of each dose tested. Unlike algorithmic methods, at each step, all of the available data is used to update the dose-response curve. This approach requires defining a number of prerequisites before starting the study: i) Choice of the underlying mathematical model that link dose to efficacy/toxicity (i.e. logistic with 1 or 2 parameters), ii) Assign an initial guess regarding the probability of toxicity/efficacy to each predetermined dose level and iii) Unlike algorithmic methods, a minimum effective dose response rate and an unacceptable probability of toxicity should be fixed. Based on all the information already known for the molecule under study (preclinical data, previous study, practitioner experience), these three prerequisites must be determined jointly by the clinicians and the statistician of the study. Once the efficacy and/or toxicity outcome of the first dose has been assessed in the first cohort, a re-evaluation of the dose response curve using Bayesian estimation is performed. The next dose to administer is thereafter determined. This process continues in this way until a stable dose is obtained or predefined stopping rules are achieved.

The advantages of these modelling approaches are therefore numerous: i) The number of patients exposed to sub-therapeutic concentrations is theoretically limited, ii) The overall available information is used at each step and iii) A confidence interval around the probability

of efficacy regarding the minimum effective dose could be obtained (66). Nevertheless, these modelling methods require some expertise (i.e., choice of the mathematical model, defining prior distributions and stopping rules) and the decision rule for dose change may seem less rational to the clinician than the standard approach. Further, a model-based dose-finding study may be sensitive to the choice of the dose-range and the prior distributions. The definition of the dose-range should be derived using extrapolation from adult PK and the use of adult information from several sources have to be taken into account to better parameterize the dose-finding design (67).

Early phase clinical trials are crucial in the drug development process. New methods have been used in order to make this important phase of development even more efficient and especially in paediatric area. Phase II experimental designs are critical and several plans can be implemented. The recruitment rate is a major element that should help choosing the best plan. The dose-exposure-response relationship of the medicinal product usually is established early in development in healthy volunteers or adult patients. Hence, dose-ranging studies are in some cases not considered necessary in children. However, in cases where the exposure-response relationship in adults is unknown or cannot be assumed to be independent of age, it might be beneficial to test more dose levels in children. It is noteworthy that paediatric trials may fail due to inadequate dose selection with unanticipated differences between adult and paediatric disease processes. This would result into false negative studies when efficacy needs to be demonstrated even if it statistically powered. Furthermore, the variables that can alter the PK and/or pharmacodynamics and so the dose-response relationship have to be identified. These factors imply the need for paediatric-specific endpoints and also the development of PKPD models (68) that are essential in understanding the dose-concentration-effect relationship and providing dosing recommendations in children.

Pharmacodynamic extrapolation

Investigation of paediatric PD maturation and scaling have not been yet fully addressed. Indeed, drug effects may be in some cases more difficult to assess especially in neonates and infants (69). Furthermore, PD endpoints may be disease specific and very heterogeneous with

a lack of standards (70). The use of extrapolation should be evaluated according to the knowledge about similarity of the disease between adults and the targeted population of children. Understanding of the developmental physiology of children should be further investigated in order to fill the gap regarding the process leading to differences in PD. In the case where extensive differences in PD between adults and children or neonates are expected, the use of PKPD modelling (68)—not extrapolation—is required to reach and assess an efficacy target specifically in the population of interest. Development of disease models that consist on the visualization of the time course of disease in individual patients under treated and untreated conditions is also a good strategy. Indeed, there is a growing amount of literature about disease progression models and drug effects upon them especially in adults. However, development of specific paediatric disease models is currently still limited as there is very little information and data available from which to build these models. Regulatory authorities could play a major role since they are in control of the largest repository of information available. Paediatric specific PKPD/Disease models could allow putting into perspective the pharmacokinetics changes occurring throughout childhood and assessing their impact on the disease progression.

General suggestions and conclusion

A standard practice in paediatric modelling should be encouraged and contribute to the regulatory science. The state of the art of modelling and simulation techniques using all available data together with advanced study designs could facilitate research in children while getting the most out of the data at the lowest burden for participating children. A few general suggestions can be made:

- Extrapolation from adult to children via the weight-based allometric rule is acceptable for children above 5 years old.
- Paediatric PBPK is a promising tool for predicting the PK in very young children (0-5 years) and specifically in preterm neonates. The question whether PBPK modelling

should be preferred over allometry plus age-dependent maturation function should be addressed.

- For drugs likely to be required in neonates, studies should ensure an optimal number of these patients are recruited, notably with varying gestational age especially if the drug will be used for preterm neonates. Further, studies should pay attention to the balance between early PNA and late PNA for neonates within the range of GA that is of relevance of the drug of interest.
- Regarding PK sampling, since limited blood volumes can be used especially in very young children, it is crucial that sampling times are optimized to obtain accurate PK information whilst being minimally invasive in terms of sample number. It is stressed that maturation assumptions on which the optimal sampling calculations were performed will play an important role and consequently sensitivity analyses using alternative assumptions on the maturation in the PK are expected. Obviously, moving dosing or sampling times to overlap with routine blood sampling visits should be favored while still guaranteeing the accuracy and robustness of the results.
- In cases where the exposure-response relationship cannot be assumed to be the same between adults and children of all ages or in case of specific childhood disease, dose-finding studies may be needed. Modelling approaches in this type of studies case are of great interest. Development of PKPD studies are also essential in understanding the dose-concentration-effect relationship and providing dosing recommendations in children.
- Investigation of paediatric PD maturation and scaling have not been yet fully addressed. Understanding of the developmental physiology of children should be further investigated in order to fill the gap regarding the process leading to differences in PD.

In conclusion, this paper reviews current considerations on paediatric PKPD modelling approaches, and provides scientific insights and suggestions to incorporate the latest knowledge on pharmacometics and innovative approaches into paediatric drug development. This paper mainly focused on extrapolation of pharmacokinetics, rather than efficacy or

pharmacodynamics. Many drugs have multiple indications and data from another condition in the paediatric population could be also considered as basis for modelling and extrapolation. The objectives of the expert group on pharmacometrics within c4c is to disseminate expertise on modelling and simulation for paediatric drug development as well as advice on request from companies or academic investigators regarding paediatric PKPD modelling aspects of their paediatric drug development or individual trials.

Conflicts of interest

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Contributors

NB conceptualized and drafted the paper. NB, AD, CK, FF, WZ, AV, EG, JS, JMT contributed to writing and revision of the paper. AD, CK, SdW, CA, PDC, SU, AKH, IP, WZ, AV, JS critically

revised the prefinal version. All co-authors (NB, AD, CK, SdW, CA, PDC, EG, FF, SU, AKH, IP, WZ, AV, JS, JMT) revised the paper draft and approved the final text version.

1. General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. :28.

2. Anonymous. Extrapolation of efficacy and safety in paediatric medicine development [Internet]. European Medicines Agency. 2018 [cité 16 juill 2021]. Disponible sur: https://www.ema.europa.eu/en/extrapolation-efficacy-safety-paediatric-medicine-development

3. Pharmacometrics | Wiley Online Books [Internet]. [cité 2 juin 2022]. Disponible sur: https://onlinelibrary.wiley.com/doi/book/10.1002/0470087978

4. Standing JF. Understanding and applying pharmacometric modelling and simulation in clinical practice and research. Br J Clin Pharmacol. févr 2017;83(2):247-54.

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

6. McCune JS, Bemer MJ, Barrett JS, Baker KS, Gamis AS, Holford NHG. Busulfan in Infant to Adult Hematopoietic Cell Transplant Recipients: A Population Pharmacokinetic Model for Initial and Bayesian Dose Personalization. Clin Cancer Res. 1 févr 2014;20(3):754-63.

7. Jones H, Rowland-Yeo K. Basic Concepts in Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development. CPT Pharmacomet Syst Pharmacol. août 2013;2(8):e63.

8. Maharaj A, Barrett J, Edginton A. A Workflow Example of PBPK Modeling to Support Pediatric Research and Development: Case Study with Lorazepam. AAPS J. 24 janv 2013;15.

9. Wu Q, Peters SA. A Retrospective Evaluation of Allometry, Population Pharmacokinetics, and Physiologically-Based Pharmacokinetics for Pediatric Dosing Using Clearance as a Surrogate. CPT Pharmacomet Syst Pharmacol. avr 2019;8(4):220-9.

10. Liu T, Ghafoori P, Gobburu JVS. Allometry Is a Reasonable Choice in Pediatric Drug Development. J Clin Pharmacol. 2017;57(4):469-75.

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

12. Banavar JR, Maritan A, Rinaldo A. Size and form in efficient transportation networks. Nature. 13 mai 1999;399(6732):130-2.

13. Dreyer O, Puzio R. Allometric scaling in animals and plants. J Math Biol. août 2001;43(2):144-56.

14. McMahon T. Size and shape in biology. Science. 23 mars 1973;179(4079):1201-4.

15. Huang Q, Gehring R, Tell LA, Li M, Riviere JE. Interspecies allometric meta-analysis of the comparative pharmacokinetics of 85 drugs across veterinary and laboratory animal species. J Vet Pharmacol Ther. juin 2015;38(3):214-26.

16. Bouazza N, Foissac F, Fauchet F, Burger D, Kiechel JR, Treluyer JM, et al. Lopinavir/ritonavir plus lamivudine and abacavir or zidovudine dose ratios for paediatric fixed-dose combinations. Antivir Ther. 2015;20(2):225-33.

17. Anderson BJ, Holford NHG. Understanding dosing: children are small adults, neonates are immature children. Arch Dis Child. sept 2013;98(9):737-44.

18. 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. avr 2014;53(4):327-46.

19. Jones HM, Chen Y, Gibson C, Heimbach T, Parrott N, Peters SA, et al. Physiologically based pharmacokinetic modeling in drug discovery and development: a pharmaceutical industry perspective. Clin Pharmacol Ther. mars 2015;97(3):247-62.

20. Yellepeddi V, Rower J, Liu X, Kumar S, Rashid J, Sherwin CMT. State-of-the-Art Review on Physiologically Based Pharmacokinetic Modeling in Pediatric Drug Development. Clin Pharmacokinet. janv 2019;58(1):1-13.

21. Leong R, Vieira MLT, Zhao P, Mulugeta Y, Lee CS, Huang SM, et al. Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. Clin Pharmacol Ther. mai 2012;91(5):926-31.

22. Malik PRV, Edginton AN. Physiologically-Based Pharmacokinetic Modeling vs. Allometric Scaling for the Prediction of Infliximab Pharmacokinetics in Pediatric Patients. CPT Pharmacomet Syst Pharmacol. 2019;8(11):835-44.

23. 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.

24. Zhou W, Johnson T, Xu H, Cheung S, Bui K, Li J, et al. Predictive Performance of Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling of Renally Cleared Drugs in Children. CPT Pharmacomet Syst Pharmacol. sept 2016;5(9):475-83.

25. 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. déc 2018;45(6):765-85.

26. 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. 29 nov 2018;21(1):8.

27. Basu S, Lien YTK, Vozmediano V, Schlender JF, Eissing T, Schmidt S, et al. Physiologically Based Pharmacokinetic Modeling of Monoclonal Antibodies in Pediatric Populations Using PK-Sim. Front Pharmacol. 2020;11:868.

28. Shepard T, Scott G, Cole S, Nordmark A, Bouzom F. Physiologically Based Models in Regulatory Submissions: Output From the ABPI/MHRA Forum on Physiologically Based Modeling and Simulation: PBPK Models in Regulatory Submissions. CPT Pharmacomet Syst Pharmacol. avr 2015;4(4):221-5.

29. Jones H, Rowland-Yeo K. Basic concepts in physiologically based pharmacokinetic modeling in drug discovery and development. CPT Pharmacomet Syst Pharmacol. 14 août 2013;2:e63.

30. Maharaj AR, Edginton AN. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. CPT Pharmacomet Syst Pharmacol. 22 oct 2014;3:e150.

31. Lin W, Yan JH, Heimbach T, He H. Pediatric Physiologically Based Pharmacokinetic Model Development: Current Status and Challenges. Curr Pharmacol Rep. 1 déc 2018;4(6):491-501.

32. Verscheijden LFM, Koenderink JB, Johnson TN, de Wildt SN, Russel FGM. Physiologically-based pharmacokinetic models for children: Starting to reach maturation? Pharmacol Ther. juill 2020;211:107541.

33. Salem F, Abduljalil K, Kamiyama Y, Rostami-Hodjegan A. Considering Age Variation When Coining Drugs as High versus Low Hepatic Extraction Ratio. Drug Metab Dispos Biol Fate Chem. juill 2016;44(7):1099-102.

34. Nordmark A. PBPK submissions and review experience in EMA and EMA draft guideline. https://www.fda.gov/media/104629/download IQ Consortium 2017.

35. Zhao P. Report from the EMA workshop on qualification and reporting of physiologically based pharmacokinetic (PBPK) modeling and simulation. CPT Pharmacomet Syst Pharmacol. févr 2017;6(2):71-2.

36. Calvier EAM, Krekels EHJ, Välitalo PAJ, Rostami-Hodjegan A, Tibboel D, Danhof M, et al. Allometric Scaling of Clearance in Paediatric Patients: When Does the Magic of 0.75 Fade? Clin Pharmacokinet. mars 2017;56(3):273-85.

37. Khalil F, Läer S. Physiologically based pharmacokinetic modeling: methodology, applications, and limitations with a focus on its role in pediatric drug development. J Biomed Biotechnol. 2011;2011:907461.

38. Abduljalil K, Pan X, Pansari A, Jamei M, Johnson TN. A Preterm Physiologically Based Pharmacokinetic Model. Part I: Physiological Parameters and Model Building. Clin Pharmacokinet. avr 2020;59(4):485-500.

39. Abduljalil K, Pan X, Pansari A, Jamei M, Johnson TN. Preterm Physiologically Based Pharmacokinetic Model. Part II: Applications of the Model to Predict Drug Pharmacokinetics in the Preterm Population. Clin Pharmacokinet. avr 2020;59(4):501-18.

40. Völler S, Flint RB, Simons SHP, Knibbe CAJ. Comment on: « Preterm Physiologically Based Pharmacokinetic Model, Part I and Part II ». Clin Pharmacokinet. mai 2021;60(5):677-9.

41. Nj V, Jm B, M de H, Mg M, Cw V, Is J, et al. Inflammation and Organ Failure Severely Affect Midazolam Clearance in Critically Ill Children. Am J Respir Crit Care Med. 1 juill 2016;194(1):58-66.

42. Balbas-Martinez V, Michelet R, Edginton AN, Meesters K, Trocóniz IF, Vermeulen A. Physiologically-Based Pharmacokinetic model for Ciprofloxacin in children with complicated Urinary Tract Infection. Eur J Pharm Sci Off J Eur Fed Pharm Sci. 1 févr 2019;128:171-9.

43. Ollivier C, Thomson A, Manolis E, Blake K, Karlsson KE, Knibbe CAJ, et al. Commentary on the EMA Reflection Paper on the use of extrapolation in the development of medicines for paediatrics. Br J Clin Pharmacol. 2019;85(4):659-68.

44. Calvier EAM, Krekels EHJ, Johnson TN, Rostami-Hodjegan A, Tibboel D, Knibbe CAJ. Scaling Drug Clearance from Adults to the Young Children for Drugs Undergoing Hepatic Metabolism: A Simulation Study to Search for the Simplest Scaling Method. AAPS J. 8 mars 2019;21(3):38.

45. Holford N, Heo YA, Anderson B. A pharmacokinetic standard for babies and adults. J Pharm Sci. sept 2013;102(9):2941-52.

46. Tang BH, Wu YE, Kou C, Qi YJ, Qi H, Xu HY, et al. Population Pharmacokinetics and Dosing Optimization of Amoxicillin in Neonates and Young Infants. Antimicrob Agents Chemother. févr 2019;63(2):e02336-18.

47. Anderson BJ, Allegaert K, Van den Anker JN, Cossey V, Holford NHG. Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance. Br J Clin Pharmacol. janv 2007;63(1):75-84.

48. Jacqz-Aigrain E, Leroux S, Thomson AH, Allegaert K, Capparelli EV, Biran V, et al. Population pharmacokinetic meta-analysis of individual data to design the first randomized efficacy trial of vancomycin in neonates and young infants. J Antimicrob Chemother. 1 août 2019;74(8):2128-38.

49. Germovsek E, Lutsar I, Kipper K, Karlsson MO, Planche T, Chazallon C, et al. Plasma and CSF pharmacokinetics of meropenem in neonates and young infants: results from the NeoMero studies. J Antimicrob Chemother. 1 juill 2018;73(7):1908-16.

50. 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. juill 2012;56(7):3833-40.

51. Kane Z, Gastine S, Obiero C, Williams P, Murunga S, Thitiri J, et al. IV and oral fosfomycin pharmacokinetics in neonates with suspected clinical sepsis. J Antimicrob Chemother. 18 juin 2021;76(7):1855-64.

52. 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. août 2016;60(8):4869-77.

53. Germovsek E, Osborne L, Gunaratnam F, Lounis SA, Busquets FB, Standing JF, et al. Development and external evaluation of a population pharmacokinetic model for continuous and intermittent administration of vancomycin in neonates and infants using prospectively collected data. J Antimicrob Chemother. 1 avr 2019;74(4):1003-11.

54. Salem F, Johnson TN, Hodgkinson ABJ, Ogungbenro K, Rostami-Hodjegan A. Does "Birth" as an Event Impact Maturation Trajectory of Renal Clearance via Glomerular Filtration? Reexamining Data in Preterm and Full-Term Neonates by Avoiding the Creatinine Bias. J Clin Pharmacol. 2021;61(2):159-71.

55. Dumont C, Lestini G, Le Nagard H, Mentré F, Comets E, Nguyen TT, et al. PFIM 4.0, an extended R program for design evaluation and optimization in nonlinear mixed-effect models. Comput Methods Programs Biomed. mars 2018;156:217-29.

56. Charles B. Population pharmacokinetics: an overview. [cité 28 juin 2021]; Disponible sur: https://www.nps.org.au/australian-prescriber/articles/population-pharmacokinetics-an-overview

57. Leroux S, Turner MA, Guellec CBL, Hill H, van den Anker JN, Kearns GL, et al. Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design. Clin Pharmacokinet. déc 2015;54(12):1273-85.

58. Germovsek E, Barker CIS, Sharland M, Standing JF. Pharmacokinetic-Pharmacodynamic Modeling in Pediatric Drug Development, and the Importance of Standardized Scaling of Clearance. Clin Pharmacokinet. janv 2019;58(1):39-52.

59. Standing JF, Anderson BJ, Holford NHG, Lutsar I, Metsvaht T. Comment on Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design. Clin Pharmacokinet. déc 2015;54(12):1287-8.

60. Qi H, Kou C, Qi YJ, Tang BH, Wu YE, Jin F, et al. Population pharmacokinetics and dosing optimization of latamoxef in neonates and young infants. Int J Antimicrob Agents. 1 mars 2019;53(3):347-51.

61. Zhao Y, Yao BF, Kou C, Xu HY, Tang BH, Wu YE, et al. Developmental Population Pharmacokinetics and Dosing Optimization of Cefepime in Neonates and Young Infants. Front Pharmacol. 4 févr 2020;11:14.

62. 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. 1 nov 2011;128(5):e1242-9.

63. Doussau A, Geoerger B, Jiménez I, Paoletti X. Innovations for phase I dose-finding designs in pediatric oncology clinical trials. Contemp Clin Trials. mars 2016;47:217-27.

64. O'Quigley J, Shen LZ. Continual reassessment method: a likelihood approach. Biometrics. juin 1996;52(2):673-84.

65. Zohar S, O'Quigley J. Optimal designs for estimating the most successful dose. Stat Med. 30 déc 2006;25(24):4311-20.

66. Zohar S, Chevret S. The continual reassessment method: comparison of Bayesian stopping rules for dose-ranging studies. Stat Med. 15 oct 2001;20(19):2827-43.

67. Petit C, Samson A, Morita S, Ursino M, Jullien V, Comets E, et al. Unified approach for extrapolation and bridging of adult information in early-phase dose-finding paediatric studies. Stat Methods Med Res. juin 2018;27(6):1860-77.

68. Mager DE, Wyska E, Jusko WJ. Diversity of mechanism-based pharmacodynamic models. Drug Metab Dispos Biol Fate Chem. mai 2003;31(5):510-8.

69. Anderson BJ, Holford NHG. Understanding dosing: children are small adults, neonates are immature children. Arch Dis Child. sept 2013;98(9):737-44.

70. Kelly LE, Sinha Y, Barker CIS, Standing JF, Offringa M. Useful pharmacodynamic endpoints in children: selection, measurement, and next steps. Pediatr Res. juin 2018;83(6):1095-103.

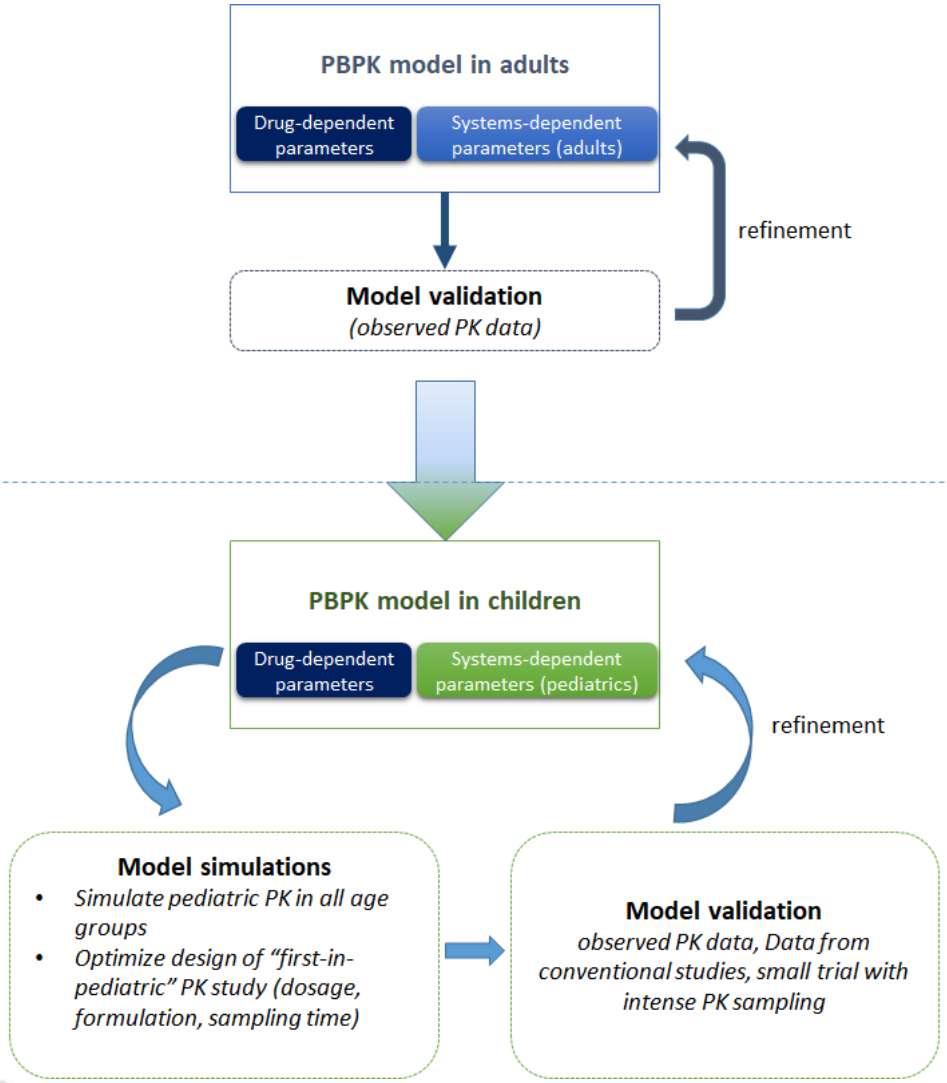

Figure 1. Exposure-matching between adults and children according to linearity assumption between drug clearance and bodyweight (left panel) or according to 3/4 allometry based assumption (right panel). A previous lamivudine popPK model in children (16) was used to simulate an adult aged 18 years, weighting 70 kg, receiving 300 mg QD (blue curve) and a child aged 5 years, weighting 18 kg, receiving either an equivalent mg/kg adult dose (red curve) or an allometric adjusted dose (green curve).

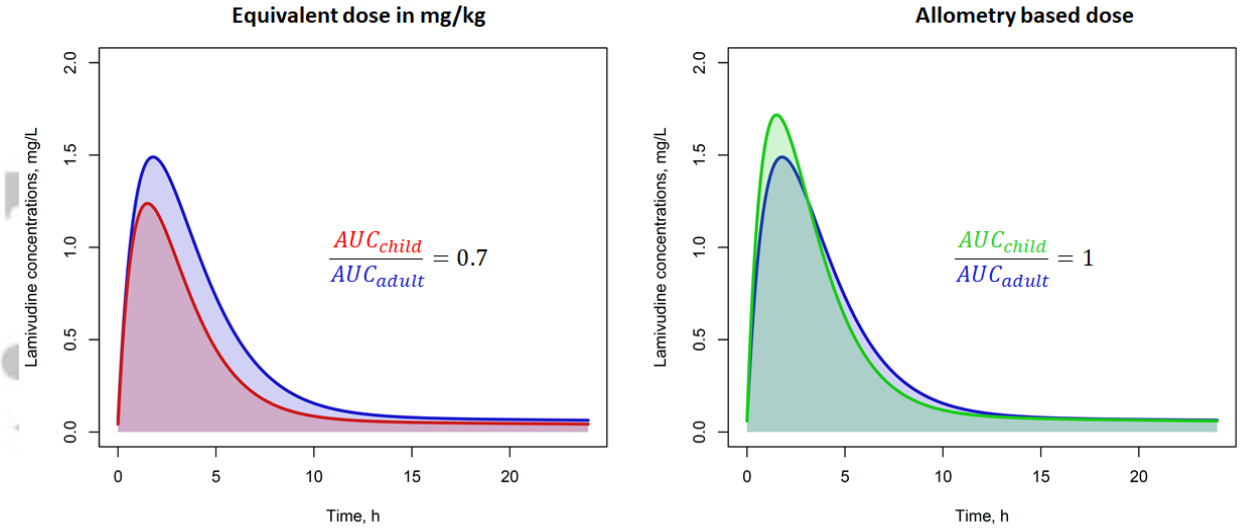

Figure 2. Schematic representation of the workflow for paediatric PBPK model development and evaluation (adapted from Leong et al.(21)).

Table 1. Differences between population pharmacokinetic and physiologically based pharmacokinetic models

Population pharmacokinetics	Physiologically based pharmacokinetics
Based on observed in vivo data ("top down")	Based on physiology of targeted specie ("bottom up")
No use of data generated in vitro	Possible to incorporate in vitro tests (protein binding, log P…)
Virtual volumes	Compartment volumes correspond to real organ or tissue volumes
Estimate the individual variability in PK parameters and identify the sources of variability	Variability prediction for model parameters is based on an empirical process
Useful for simulation scenario, mainly constrain to the range of the available data	Useful for simulation scenario, even outside of the range of the available data

Table 2. Advantage and uncertainty regarding extrapolation tools (Allometry and physiologically based pharmacokinetic modelling).

	Advantage	***Uncertainty***
Allometry	- Easy to use (only adult clearance value needed)	- Extrapolation from adults directly to the youngest children can be considered risky
	- Fully acceptable for children more than 5-yr old	- Debate on the 0.75 exponent on clearance
		- Need of age maturation function along with allometry below the age of 2 yrs (requires additional data)
		- No variability on predictions
Physiologically based pharmacokinetic modelling	- Implementing time-varying physiology into these models	- Maturation functions often differ from one software or source to the next
	- The different elimination pathways are charaterized	- Establishing confidence in the performance of the adult PBPK model needed
	- Can be used to predict drug-drug interactions	- Model need to be refine in the building process using available data
	- Served as a valuable predictive tool for designing clinical trials and optimizing dosing regimens	- Requires a comprehensive understanding about physiological, biochemical and physicochemical processes
	- Can be used to predict different route of administrations	- Requires knowledge of the drug properties (information on all elimination routes, enzymes and transporters involved, plasma protein binding to albumin/α1-acid glycoprotein, etc.)
		- Variability prediction for model parameters is based on an empirical process