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Does size matter? : bridging and dose selection in paediatric trials

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Chapter 2

Scope and intent of investigation

PAEDIATRIC DRUG DEVELOPMENT has recently become a major milestone in R&D. Historically, paediatric plans have been treated as a replica of the adult programme, except for the empirical adjustment of the dosing regimen [1]. In fact, information obtained from adult subjects has been used as reference for evaluating pharmacokinetics, pharmacodynamics and safety in children even when disease conditions do not occur in adults. Such an approach neglects the role of developmental changes and disease pathophysiology, which can have pronounced effects on absorption and disposition processes as well as on the resulting pharmacological effect [2, 3]. Given the numerous challenges in the implementation of clinical trials involving children, it is imperative that data generated to support the use of new chemical and biological entities in children account for the aforementioned processes, yielding appropriate dosing recommendations *before* any efforts are made to show evidence of efficacy and safety.

Dose scaling in paediatric trials remains an empirical exercise both from a clinical perspective and from a drug development standpoint. A model-based approach is proposed in this thesis to address the main issue underlying paediatric drug development, i.e., the dose rationale for trials in early clinical development. In contrast to empirical methods, which rely on scaling factors as the basis for the extrapolation of the dose across age groups, non-linear mixed effects modelling relies on parameter distributions to assess potential differences between adults and children. Dose recommendations can then be derived taking into account size, (patho)physiological factors and uncertainty in a systematic manner. Moreover, hierarchical models allow the use of simulations to explore the implications of different dosing regimens on drug exposure, response and consequently improve trial design. Given the known difficulties in running clinical trials in children, it is also of interest to explore the value of inferential methods to support data extrapolation based on the parameter distributions obtained from such models.

The dose rationale in paediatric indications must take into account differences

in pharmacokinetics (PK), pharmacodynamics (PD), disease or a combination of these factors. Pharmacokinetics may differ from adults for several reasons: variability due to age, gender, body composition, anatomy and physiology. The latter factor includes differences in liver and renal function as well as maturation (ontogeny) and metabolic capacity associated with enzymatic systems, which vary throughout the life span from neonates to adults. A discussion of the differences due to pharmacodynamic factors and disease will remain beyond the scope of our work. This thesis will be based on the assumption that efficacy can be warranted only if comparable exposure is achieved between populations.

Since children may not be subject to dose escalation studies similar to those carried out in the adult population, some initial estimation of the dose in children must be obtained by extrapolation or inference. Here we delve into the opportunities for implementing bridging studies, which provide the rationale for dose and dosing regimen based on the expected differences in pharmacokinetics across populations. Bridging concepts form the basis upon which inferences can be made about efficacy and safety under the assumption that parameter distributions accurately capture the effect of differences in size and (patho)physiology. As such, these pharmacokinetic studies can have major impact on dose selection and consequently on the overall paediatric development programme. This thesis will also focus on how optimality principles and flexible protocol designs can be applied to mitigate uncertainty in parameter distributions, ensuring accurate dosing recommendations in early clinical development.

We will show that in defining dose recommendations, the challenge is to identify one or more physiologically meaningful factors that can be used as surrogate for the changes associated with developmental growth, including the role of maturation and the consequent increase in metabolic capacity. Ideally, such a surrogate should enable dose adjustment based on a reference group (e.g. adults), allowing for interpolation and extrapolation of pharmacokinetics across all paediatric ages. This last requisite also implies bi-directionality, i.e., one should be able to describe the changes due to developmental growth not only from adolescents to neonates but also from neonates to adolescents.

For the purposes of bridging, the assumption of similar exposure-response relationships between adult and children implies that differences in physiological processes between adults and children must be taken into account when selecting the paediatric dose. The most common method for dose adjustment in children in paediatric clinical practice is to normalise the adult dose by body weight (i.e. mg/kg), assuming a linear relationship between weight and dose. Other methodologies assume other covariates as scaling factors, like age or body surface area. Non-linear relationship between pharmacokinetic parameters and demographic covariates empirically proved to be more reliable [4–8]. However, no matter which covariate is used, there is a common problem for these scaling approaches: all of them assume the effect of a covariate on the parameter without prior assessment of which physiological factors alter pharmacokinetics and how these (might) differ across the paediatric population. An immediate consequence of this approach is the unidirectional nature of scaling: children will always get lower doses than adults,

when it is well known this is not always the case.

On the other hand, one must bear in mind that the adjustment of the dosing regimen is necessary, but not sufficient to provide children with the best treatment option. Pharmaceutical formulation and route of administration are important factors that need to be considered as they can alter pharmacokinetic parameter distributions and overall drug exposure, irrespective of differences in size or metabolic function [9, 10]. For instance, modified release formulations can be sensitive to differences in transit time and pH. These issues will not be addressed in this thesis, but can be handled as another cause of uncertainty.

From a methodological perspective, the challenge for a more mechanistic scaling of the dose is amplified by the limited use of appropriate mathematical and statistical tools. There are a few specific issues that need to be addressed when characterising pharmacokinetics in children. The first is the poor precision of parameter estimation, caused by the paucity of data combined with the use of traditional data analysis methods: sparse sampling and small populations are often used in paediatric trials [11]. Non-compartmental data analysis methods are not suitable or recommended under these conditions. The second is the choice for the parameterisation of pharmacokinetic processes in a way that changes due to developmental growth can be accurately described [12]. An ideal bridging strategy should cope with these issues, i.e., it should provide reliable estimates despite the limited availability of data and enable correct parameterisation of the effects of covariates. Moreover, it would be valuable if it enabled extrapolation of the results beyond the available data to different populations.

Tools are available that support a less empirical correction of required dose and dosing regimen in children, using a fully parametric approach to adjust for differences between populations. Among others, non-linear mixed effects modelling can be applied to assess pharmacokinetic parameters and establish their correlation with weight, age and other relevant demographic covariates. However, a population pharmacokinetic model itself may not be sufficient to provide accurate estimates for the paediatric dose. Demographic covariates often lack the ability to correct for differences in metabolic capacity if ontogenic processes are involved. This is especially true for infants, i.e. <2 years old [13]. Instead of merely scaling pharmacokinetic parameters based on the relative size of children, we propose the concept of **scaling for function**. The concept of scaling for function is based on inferences from pharmacokinetic parameter distributions in children without making *a priori* assumptions about the correlation between parameters and demographic covariates. This is comparable to the rationale for assessing drug exposure in other special populations such as obese and hepatically impaired patients. In addition, this approach allows one to tackle another issue in paediatric pharmacology, i.e., the assumption that the correlation between pharmacokinetic parameter and demographic covariates remains invariant throughout the whole age range from birth to adolescence.

The investigations described in this thesis illustrate therefore the development of a modelling strategy for bridging in early clinical trials, which does not only enable better parameter estimation taking into account historical data, but also

provides a pragmatic solution for the lack of predictive value of current modelling parameterisation when ontogeny and disease factors are not common across the populations of interest. Four different drugs were evaluated, namely abacavir, midazolam, atovaquone and proguanil. The aim was to demonstrate the application of the methodology to a broad range of drugs irrespective of their pharmacokinetic properties or physicochemical and metabolic profiles.

Finally, we also make clear that even when a model-based approach is applied and parameters distributions are estimated with good precision and accuracy, such results do not translate directly into dosing recommendations or dose rationale. We apply simulations to translate pharmacokinetic parameters into dosing recommendation in children. Simulation scenarios are necessary to ensure that bridging requirements are met as well as to account for the implications of different sources of variability and uncertainty. In conjunction with flexible protocol designs, the proposed approach enables discrimination and mitigation of the impact of uncertainty in parameter estimation due to covariate effects from the uncertainty caused by the paucity of data and eventual bias in the scaling methodology (i.e., model misspecification). In practice, we demonstrate that the first dose to be administered in a clinical trial should be predicted by model-based scaling of data followed by a re-estimation step, during which doses are adapted individually in order to account for uncertainty, model misspecification and other factors, such as formulation differences. In this respect, it should be highlighted that flexible protocols can be valuable for the optimisation of the dosing regimen not only in bridging studies in children, but also in PKPD, dose ranging, efficacy and safety trials.

2.1 Introduction

In **Chapter 1**, an overview is given of the approaches currently used for the selection of the paediatric dose, including their flaws and limitations. The possibility of applying model-based methodologies is subsequently discussed and modelling and simulation concepts highlighted as a tool for dose regimen adjustment in children.

The issue of paediatric dose selection arises from the off-label use of drugs in children. This means that paediatric patients are treated according to a regimen which has not been formally tested for efficacy and safety or given to a patient group who was not included in the label or summary of product characteristics. Historically, this is due to the lack of randomised controlled trials in children and due to the empiricism associated with dose rationale in clinical practice. Dose adjustment is often based on the assumption of *a priori* relationship between size and the physiological factors which determine drug exposure. Here we emphasise the concept of scaling for **function** instead of scaling for **size**, i.e. the dose rationale should be based on the evidence of the potential effects of physiological factors and developmental growth on pharmacokinetics instead of a pre-defined assumption about the influence of size as covariate. Size matters only when it is a surrogate for differences in physiological function.

The concept of bridging is presented as the basis for inferences about drug efficacy, under the assumption of common PKPD relationships and disease across populations. In conjunction with the use of a model-based approach, bridging offers a unique opportunity to dose optimisation in paediatric indications. From a methodological standpoint, parameterisation of drug disposition and physiological factors using hierarchical models represents a critical step for the implementation of the approach. Although this thesis will focus on the bridging from adults to children, we envisage that this concept can be easily adapted to other applications, such as bridging across paediatric groups, ethnicities and pathological conditions.

Lastly, special attention has been given to the discussion of pros and cons of allometry, allegedly reputed as the most mechanistic scaling methodology available at the moment. The relationship between the physiological parameters which determine drug exposure and demographic covariates, such as body weight, age, etc. has been challenged on a theoretical and on a practical basis. The assumption of a linear or exponential relationship between pharmacokinetics and demographic covariate imposes a lower dose in children compared to adults. We show numerous examples where such a relationship does not hold.

2.2 Parameter estimation and uncertainty

The second part of this thesis focuses on the requirements for accurate parameter estimation and explores methods for better identifying differences in parameter distributions. This will represent the basis for scaling the dose and dosing regimens across populations. Despite existing examples of the application of pharmacokinetic bridging in drug development, no formal evaluation has been made of pre-requisites and performance of the approach. One of the main concerns is the accuracy and bias in parameter estimation due to the sparse number of samples and limited number of patients participating in early clinical trials. Pharmacokinetic data from Phase I, II and III clinical trials were therefore investigated retrospectively to test the suitability of a model-based approach as the method of choice for identifying the correct paediatric dose. Focus is given to the implications of variable sample size in data analysis as well as on the effect of different random and non-random inter-individual variability on pharmacokinetic parameter estimation.

Another important aspect is the predictive performance of models taking into account the limitations of allometric scaling concepts and of the choice of parameterisation other than size to describe the effects of developmental growth and physiological function. The use of adult data as the basis for data extrapolation implies that differences are primarily driven by the magnitude of parameter estimates, but that the structural components (fixed effects) determining drug disposition across populations are comparable. This assumption means that the contribution of a common biological substrate from birth to adolescence and that a common relationship between parameter and covariates must hold across the various age groups. These concepts are challenged throughout various chapters in this thesis. To this purpose, maximum likelihood estimation methods are used in conjunction

with informative and non-informative priors to offset the limited availability of data in the population of interest. The aforementioned points contrast with the common belief that the non-compartmental analysis of pharmacokinetic data and rich sampling schemes are sufficient to characterise and explain differences between populations. We show that the use of non-compartmental analysis imposes major limitations not only to the protocol design (i.e., sample size), but also the interpretation of findings. In addition, we highlight that the availability of parameter estimates does not automatically translate into dosing regimen recommendation. This represents one of the main shortcomings of model-based analysis of paediatric data. Without comprehensive use of simulations in which variables of interest rather than model parameters are taken into account, one cannot define the correct dose for children and concomitantly demonstrate whether a proposed dosing regimen meets bridging requirements.

In **Chapter 3**, we investigate the use of parameter distributions as the basis for the characterisation of pharmacokinetics in children and the implication of different trial design factors and pharmacokinetic properties. Using compartmental models and a range of scenarios for different drug, population and design features, simulations are used to determine the accuracy and precision of differing parameter point estimates. This informal sensitivity analysis may be considered a proof of concept for the methodology applied later in this thesis. We have assessed the impact of sampling frequency and group size on parameter estimation. Hypothetical compounds with different pharmacokinetic properties were considered that mimic one-compartment disposition with intravenous or first-order absorption, two-compartment disposition with first-order absorption and Michaelis-Menten elimination kinetics. Data were simulated and re-fit to a population pharmacokinetic model. Different scenarios were developed to explore how sampling frequencies and group sizes impact on the estimation of pharmacokinetic parameters in children.

Although an infinite number of scenarios could have been simulated, we have prioritised a few conditions, which are clinically relevant for the subsequent evaluation of a model-based approach for the purpose of pharmacokinetic bridging. The scenarios included different sampling schemes (3, 4, 5 or >5 samples per subject), population size (5, 10, 20 or more subjects), pharmacokinetic parameters, parameter ranges (values ranging from 10% to +400% compared to the reference population) and inter-individual variability (from 10% to +50%). The criterion for the acceptance or rejection of the models was the ability to discriminate between adult and paediatric population. Model performance was assessed using the objective function value and the relative errors of the parameter estimates. Based on the various scenarios described above, the degree of bias and precision was assessed, and consequently the minimum number of patients to be included in a hypothetical trial, together with the number of samples required, was determined. Overall, these simulations allow the identification of the most sensitive conditions for parameter estimation. Of particular interest is to understand whether frequent sampling is required to assess differences in pharmacokinetics and the threshold to identify them. It is also important to demonstrate whether pharmacokinetic parameter distributions from a reference population can be used to determine population

size and sampling scheme in a paediatric trial, instead of relying on best guess or empiricism.

From a methodological perspective, when dealing with a new paediatric population, one can approach the issue of bridging assuming comparable parameter distributions between adults and children, and demonstrate whether or not this is the case. Alternatively, one could assume different parameter distributions between populations and then quantify how much they differ. In either case, it is desirable to have an anchoring point for parameter estimation. Such an anchoring point can be directly obtained by the concurrent analysis of individual adult and paediatric data, so that the reference group directly contributes to the maximum likelihood during model fitting, or indirectly by the introduction of informative or non-informative priors in a Bayesian hierarchical model. To address this issue, in **Chapter 4** adult data from Phase I and II clinical trials with abacavir (111 subjects) were combined with sparse data from children enrolled on an efficacy trial (14 subjects with age ranging from 2 to 13 years). A model-based analysis is proposed to characterise differences in parameter distributions and implications for the exposure to abacavir. Different approaches are considered to tackle the question of uncertainty and identifiability of parameter distributions when limited data is available. Specifically, we explore the role of dichotomisation by age, pooling of historical adult data and the use of Bayesian priors for fixed and random effects. Given the nature and specificity of the metabolic elimination of abacavir, it is also possible to illustrate how to optimally characterise the non-linearity in the correlation between pharmacokinetic parameters and demographic covariates, which are often used as surrogate or descriptors of developmental growth. Simulations were subsequently used to evaluate the impact of different dosing regimens on the overall systemic exposure (i.e. area under the concentration-time curve, AUC) and identify which ones warrant drug levels comparable to the reference values in adults.

Another important methodological aspect regards the uncertainty and accuracy of extrapolations based on model parameters estimates. Of particular interest is to establish the influence of developmental factors on the covariate model structure, as those may differ considerably across age groups in which maturation of the metabolic capacity may play a more predominant role than size. Paramount is to identify whether parameter-covariate correlations hold true beyond the range supported by the data. Such a correlation ultimately determines the predictive value of a model and, consequently, the accuracy of the extrapolations of the dosing regimen from one population to another. The implications of such a requirement were evaluated in **Chapter 5**. Our analysis shows that the predictive performance of a model is critical for early clinical development, during which the main objective is to characterise the pharmacokinetic properties of a drug in a population yet to be investigated. Based on the model built in **Chapter 4** and another model using data from 23 infants (3-36 months old), we illustrate how extrapolations can be made to a different group using simulations. We explore the importance of simulating patients which have different covariate values than those in the real data and the impact of such difference on parameter distribution predictions. In fact,

we replace the external validation of the model in a small subgroup belonging to the same population of the initial data, with the assessment of model performance in a hypothetically larger population.

In **Chapter 6**, we assess the performance of model parameters to make interpolations between populations. One of the main issues that remains overlooked by supporters of model-based methods in paediatric drug development is how to best account for data imbalance and lack of formal stratification of the population by a predefined (demographic) covariate, such as age or body weight. Here we focus on the issues underlying the selection of the covariate model and the accuracy in the estimation of parameter distributions within and across different paediatric populations. The challenge is the identification of a common descriptor for the changes in physiological function, which accounts for the (variable) contribution of maturation (ontogeny), increase in metabolic capacity and developmental growth (size) across the various paediatric groups. This issue is investigated using midazolam as a paradigm compound. Midazolam pharmacokinetics is well-characterised in humans and so is the ontogeny of CYP3A4 isozymes, which determine drug elimination. In contrast to the model building procedures used for abacavir (**Chapter 4**), data from adult patients and infants and toddlers (<25 months old) were fitted to an allometric model, in which a predefined value is imposed for the exponent describing the correlation between parameters and covariates. This allometric model was used to interpolate pharmacokinetic parameters in the group between the two aforementioned populations (i.e., children and adolescents). Based on allometry concepts, this intermediate group can be considered part of a continuum in terms of developmental growth, and therefore, allometric models should predict midazolam exposure in the population of interest. As previously described in **Chapter 5**, we evaluate model performance by comparing predicted drug exposure based on interpolation by the allometric model with the results obtained by the model built on the data from 18 children and adolescents. The predicted exposure should not be different under the assumption that the covariate-parameter correlation remains constant in both groups.

From a statistical perspective, the modelling issues described in **Chapters 4, 5 and 6** also illustrate the limitations of maximum likelihood methods. The choice of parameterisation in general (fixed and random effects) and the covariate selection are determined by model diagnostics (goodness-of-fit) which assess model performance relative to the available data, making models primarily descriptive, rather than mechanistic or predictive. We explore the relevance of bootstrapping and simulation scenarios, including different conditions (patient, sample size, dose range) from those used during model building. Albeit limited, the evaluation of Bayesian priors highlights the implications of an alternative methodology to ensure the appropriate use of inferences for pharmacokinetic bridging.

Another important issue in terms of bridging is the requirements for dosing recommendations when drug combinations are used. Currently, drug combinations based on a fixed ratio between doses are widely used in adults and as such extrapolated to paediatric indications. In **Chapter 7**, we investigate how to best scale doses from adults to children for a combination of two or more different drugs. We

also assess the implications of maintaining a fixed ratio between the active moieties across the various paediatric subpopulations. From a modelling perspective, this exercise shows the importance of taking formulation and pharmaceutical factors into account, i.e., dose strength and dosage form as integral components of a bridging strategy. This concept is illustrated using the combination of atovaquone (ATV) and proguanil (PGN), both active compounds in the treatment and prevention of *Plasmodium Falciparum* malaria in adults and children. We show how the use of tablets of different strengths, but fixed ratio between ATV and PGN affects systemic exposure in children. In this case, it is not the paucity of the data that represents a challenge for model building and parameter estimation. Instead, it is the identification of the appropriate covariates affecting the pharmacokinetics and their effect on dosing recommendations. For the characterisation of the exposure to ATV and PGN, the role of ethnicity is as important as the role of body weight. Using simulation scenarios similar to those described in Chapter 4, we show that the use of fixed-dose ratios imposes an implausible assumption, i.e., that the relationship between parameters and covariates for both moieties is the same. At the same time, we explore the implications of additional (unknown) covariates on parameter distributions in children. The so-called predictive performance of a model is questioned as such factors cannot be considered during model building. A different approach is required in which model uncertainty is incorporated into the prediction of drug exposure across populations.

2.3 Protocol implementation and trial design factors in paediatric trials

In this part, we proceed from the theoretical concepts underlying parameter estimation and dose selection to the requirements for the design and implementation of paediatric protocols for pharmacokinetic bridging.

Despite some initial estimation of the dose in children, which may vary depending on the assumptions about the effect of developmental growth factors, the magnitude of the differences in parameter distribution across population and the correlations between parameter and covariates, other aspects need to be considered for establishing accurate final dosing recommendations. Among others, attention should be paid to pharmaceutical factors and to time-varying parameter-covariate correlations. Dosage form and formulation differences need to be factored as well, given that they may alter systemic drug exposure. The use of bioequivalence tests in adults, as currently performed, does not suffice to predict the effects of pharmaceutical factors in children. In addition, as highlighted previously, demographic covariates may not be fully predictive of the changes in function, which ultimately determine the differences in pharmacokinetics in children. In such cases, limitations exist in the predictive performance of a model when used for extrapolation and interpolation purposes.

Whilst mechanistic models remain to be found and may not be available

before the next decade, a strategy must be devised during the implementation of clinical studies which tackles the issue of uncertainty in parameter estimation and in covariate-parameter correlations. For that purpose, one should consider the benefits of flexible trial protocols, including adaptive designs, to implement bridging concepts effectively and ensure the appropriate dose selection in children. This requirement becomes even more important when PKPD relationships and efficacy must be assessed in addition to pharmacokinetics.

Often the use of rigid, non-adaptive protocols is considered best practice in regulatory (confirmatory) trials, during which efficacy is to be demonstrated. In these circumstances, a predefined dose is selected irrespective of the individual differences in exposure. It is the difference in response between treatment arms that matters. This concept seems to have permeated paediatric development, in that confirmatory designs are proposed in early clinical development, without first addressing the rationale for dose selection and the issue of parameter uncertainty. It should be clear that in contrast to efficacy trials, it is drug exposure that matters if pharmacokinetic bridging studies are to be performed. In **Chapter 8** we assess therefore the advantages of using a randomised concentration-controlled trial (RCCT) as compared to a typical fixed dose protocol design. Instead of randomising patients to a dose level, in a RCCT patients are randomised to a pre-defined exposure range. Drug levels are monitored after an initial dosing regimen and titration steps are used to adjust exposure according to randomisation, if necessary. This approach reduces the impact of random factors on pharmacokinetic variability, enabling more accurate estimation of the parameters of interest, such as clearance and volume of distribution. Most importantly, the approach can also be used to support the evaluation of PKPD relationships and efficacy in indications where pharmacokinetic bridging may not be suitable.

The concept is illustrated with clinical trial simulation scenarios using the antiviral drug abacavir. Based on the pharmacokinetic model previously developed in Chapter 4, the performance of a RCCT was evaluated and compared to a fixed dose design. A putative study population of 128 paediatric patients was simulated, taking into account a broad range of weight and ages. The treatment schedule comprised three consecutive periods, during which monitoring procedures are in place to assess and adjust drug levels according to predefined bridging criteria (i.e. target exposure). After a starting dose, which is administered according to the current dosing recommendation (8 mg/kg), the dosing regimen is individually adapted, if exposure differs from the proposed randomisation range. A check point is in place to ensure that no further adaptation of the regimen is required after multiple dosing. The main objective of this investigation is to show how different protocol designs in paediatric clinical trials may be used to minimise uncertainty in the estimation of pharmacokinetic parameters of interest, which can subsequently be used to support the dose rationale. Furthermore, these procedures also illustrate how model misspecifications or wrong assumptions about parameter-covariate correlations can be corrected during the clinical trial, without compromising the outcome of the

study.

Another important application of RCCT is the optimisation of dose selection when the effect of covariates on pharmacokinetic parameters cannot or has not been characterised in the reference adult population. In these circumstances, extrapolation by allometry or other empirical methods may not warrant accurate prediction of the changes in pharmacokinetics and subsequent extrapolation of the dosing regimen to the target paediatric population. In **Chapter 9**, RCCT is applied to the development of a putative new combination of atovaquone and proguanil. In this example, we take the opportunity of demonstrating the implication of a flexible protocol design in a “first-time in children” trial, i.e. when only adult pharmacokinetic data is available at the start of the trial. Four main scenarios were considered to accurately describe the complexity in the assessment of the dose rationale for both drugs, accounting for the uncertainty in parameter distributions associated with the developmental growth. The following scenarios were considered to explore the implications of pharmacokinetic differences in the target population: a) the effect of maturation is predominant and drug clearance is therefore assumed to be reduced to 20% of the reference value; b) the effect of developmental growth (size) was predominant and clearance was assumed to be reduced on average by 50% of the reference value; c) the effect of developmental growth was counteracted by increased metabolic capacity which might occur due to co-medication, comorbidities or other intrinsic factors (e.g. phenotype) and clearance was set to be equal to the reference value in adults; d) the effect of developmental growth was allometrically correlated with body weight and clearance assumed to vary according to the differences in body weight. We focus on clearance not only because it determines systemic exposure and consequently the requirements for dose adjustments, but also to avoid long computational times. In a real patient population, the effect of developmental growth, maturation and changes in metabolic capacity can also alter pharmacokinetic parameters such as volume of distribution, absorption rate constant and bioavailability. Depending on physicochemical properties and pharmaceutical differences, they all need to be considered.

Based on an adaptive study design in which titration steps are used to ensure exposure levels according to randomisation, we explore how to optimise the dose and dosing regimen, irrespective of the cause and magnitude of changes in pharmacokinetics, which are unknown at the beginning of the trial. In these circumstances, as shown in Chapters 5 and 6, it is very likely that predictions and extrapolations made by a pharmacokinetic model based on a reference population may be biased, leading to recommended doses that may be far from optimal. This exercise ultimately illustrates that in spite of the requirements for additional visits and effective bioanalytical support, the use of titration steps according to a RCCT mitigates the issue of parameter uncertainty in paediatric trials, especially when little is known about the potential covariates affecting pharmacokinetics in the population to be tested. In other words, the use of adaptive protocols may be considered as an “insurance policy” against model misspecifications.

2.4 Conclusions and perspectives

The last part of this thesis provides an integral summary of the findings and conclusions from the investigations presented throughout the previous chapters. In **Chapter 10**, we focus on the consequences of inaccurate dose rationale for children and the implications of a model-based approach for pharmacokinetic bridging in paediatric drug development. Moreover, concrete recommendations are made for improving protocol design and data analysis of paediatric trials in which pharmacokinetics is evaluated. We acknowledge that many methodological aspects remain to be explored, which are pertinent to the assessment of pharmacokinetic properties in children, in particular when considering other types of molecules (e.g., biopharmaceuticals) or routes of administration (e.g., topical delivery). We anticipate that advancement of paediatric drug development will require further attention to the so-called *level of evidence* needed for the assessment of pharmacokinetics, safety and efficacy and how inferential methods can be applied to meet that purpose.

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