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

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Chapter 10

Summary, conclusions and perspectives

10.1 Regulatory framework and challenges in the transition from retrospective to prospective assessment of medicines for children.

THE OBJECTIVE OF MODERN PHARMACOLOGY is to improve the effectiveness of current treatments and to provide new medicines to treat as many diseases and conditions as possible. Since the 1960s, with the Kefauver-Harris amendment to the Food Drug and Cosmetic Act in the USA in 1962 [1] and the European Directive harmonising requirements for marketing authorisations in 1965 [2], the action of national and supranational governments has forced the pharmaceutical companies to provide scientific evidence on efficacy and safety of all new drugs. Since then, before any product is authorised for marketing, the medicine must have undergone extensive testing including pre-clinical tests and clinical trials to ensure that it is safe, of high quality and effective. Because of this legislation, together with the impact of evidence-based medicine, medical treatment has made considerable progress in the last fifty years. Yet, children have not profited as much as adults from the benefit of such innovations.

The reasons for this situation are complex and involve many cultural aspects and the role children have in society. No more than 40 years ago, paediatric oncologists treating paediatric patients affected by acute lymphatic leukemia with cytotoxic drug were accused of using the children as “guinea pigs”. The consequences of such an environment have led to the predominant off-label use of medicinal products in

children [3]. Nowadays, the current European legislation mandates that new drugs must be available for children once their efficacy and safety have been proved, even though public opinion is not always aware that this requires a well-thought scientific rationale and subsequently the enrolment of children on clinical trials, with all the risks related to them. In addition, it has not become yet evident to the medical community that the legislation has introduced an unprecedented revolution, forcing paediatricians to consider the future paediatric use of new chemical or biological entities, which are neither on the market, nor available to the adult population yet. This poses an important challenge: informal benchmarking from prior therapeutic utilisation in adults will not be available at the time a new drug or biological is first administered to children.

The long-lasting arguments that in the past supported the empiricism used by paediatricians and paediatric pharmacologists will have less and less space in the years to come. Off-label use will not be supported by evidence of safety and efficacy in adults at the same extent post-launch data have provided in the past. In contrast to the retrospective evaluation of a drug's pharmacokinetics, pharmacodynamics or clinical profile, which has been driven by academic research, considerations about the clinical development of new medicines and future use of a new compound in children will require direct involvement of the pharmaceutical industry and potentially other sponsors. This represents the single most important challenge to the success of this new era in paediatric drug development [4].

Despite the new regulatory environment, the theoretical and scientific framework supporting the rationale for and implementation of paediatric trials has not evolved at the same speed. The evaluation of efficacy and safety of drugs in children still relies on empirical extrapolations from clinical trials in adults.

In this thesis we have dealt with one of the basic problems in paediatric pharmacology, a challenge that must be tackled in every single trial, namely, the selection of the right dose for paediatric patients. We have shown that in defining dose recommendations, one must take pharmacokinetic-pharmacodynamic relationships into account or at least make inferences about it. Under the assumption of the need for dose adjustment due to differences in pharmacokinetics (including the role of maturation and the consequent increase in metabolic capacity), disease and physiological function, the challenge is to identify one or more clinically meaningful factors that can be used as surrogate for the changes associated with developmental growth. 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.

Instead of merely scaling pharmacokinetic parameters based on the relative size of children, we have introduced the concept of **scaling for function**. In contrast to current medical practice, our approach is based on the use of inferential methods taking into account pharmacokinetic parameter distributions in children without *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 (e.g. obese and hepatically impaired patients). In addition, we also demonstrate the flaws in 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 throughout this thesis illustrate therefore the principles and requirement for the optimisation, design and analysis of early clinical trials in children. In Chapter 1 we have highlighted the implications of empiricism as the basis for the choice of the dose in paediatric clinical trials. Different methodologies currently used to scale the dose from adults to children have been presented, including a discussion about the underlying assumption of an *a priori* relationship between dose and size. We refer to this approach as **scaling for size** (where size can be described by body weight, height, age or any other demographic covariate). Its flaws were shown using examples with different drugs. An important drawback of these scaling methods is that, with the exception of allometry, they all assume a linear correlation between dose and size, despite the evidence for non-linearity.

We then make a plea for the development of a dose rationale based on “scaling for function”. Based on the ICH-E11 guideline

When a medicinal product is to be used in the paediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and paediatric patients, and the outcome of therapy is likely to be comparable [...], pharmacokinetic studies in all the age ranges of paediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of pediatric doses that will produce blood levels similar to those observed in adults;

we have explored how to best characterise and parameterise pharmacokinetic differences between adults and children and across the whole age range of the paediatric population. Assuming similar exposure-response relationships between adults and children, the advantages of a model-based approach were considered for dose adjustment and subsequent implementation of pharmacokinetic bridging studies, in which the objective is to ensure drug exposure levels comparable to adults. From a methodological standpoint, the use of hierarchical modelling and simulation concepts represents a critical step for the implementation of the approach.

10.2 Parameter estimation and uncertainty

In Chapter 3 we explored the feasibility of characterising pharmacokinetics in children based on an integrated analysis of data from serial blood sampling in adults and sparse sampled data in children. Our simulations showed how sampling frequency and group sizes affect the estimation of pharmacokinetic parameter distributions in children. Simulated plasma concentration data from hypothetical

compounds with different PK properties were analysed using non-linear mixed-effects modelling, taking into account differences in parameter distribution and drug disposition between adults and children. Population pharmacokinetic modelling allows for the analysis of rich adult data and sparse paediatric data in an integrated manner to obtain accurate estimates of parameter distributions in children, without exposing them to a serial sampling protocol, typical of non-compartmental methods. Moreover, we demonstrate that irrespective of the pharmacokinetics of the drug, the number of patients resulted to be more important than the number of samples per patient. Not surprisingly, an increase in the complexity of the model describing the pharmacokinetic of the drug requires additional sampling and population size compared to less complicated models. Clearly, sample size must be determined as a function of the model parameterisation. This contrasts with current practice in clinical trials, for which sampling frequency and population size are determined empirically.

Based on the aforementioned findings, in Chapter 4 we explored the possibility of overcoming the requirement for larger population size and more frequent sampling schemes, by including data from a reference group to ensure accurate estimation of the pharmacokinetic parameters of interest. Using different definitions of populations and parameter distributions for adults and children, various modelling approaches were evaluated to support bridging studies and identify the best descriptor of developmental changes that can be used as covariate for dose adjustment in children. The proposed approach was illustrated for the antiviral drug abacavir, a nucleoside analogue reverse transcriptase inhibitor (NRTI) used to treat HIV infection. Unfortunately, the covariate analysis was restricted to the available demographic and physiological factors, namely body weight, age and height. Eventually, we demonstrated that priors from pharmacokinetic parameters in adults can support parameter estimation during the analysis of paediatric data. This method prevented model misspecification, yielding successful minimisations with higher precision in parameter estimates compared to other attempted approaches and represents a new methodology for the characterisation of pharmacokinetics in children. Most importantly, we have shown how simulations can be used to assess the implications of different dosing regimens and provide final dosing recommendations. The evaluation of covariate effect on parameter distributions, rather than on observed exposure, and the inclusion of priors from pharmacokinetics in adults allow for inferences about the clinical relevance of pharmacokinetic differences across populations.

In spite of the use of a model-based approach, evaluation of the relevant parameter-covariate correlations was limited to the data set available for model building. An evaluation of the dosing requirements for infants and toddlers was derived by inference, given that this paediatric subpopulation was not part of the original dataset. Drug exposure was extrapolated assuming that the same model and parameter-covariate correlations would apply across all paediatric subpopulations. This assumption was further evaluated in Chapter 5 and proved wrong when the model predictions were compared with observed exposure distributions in a population of infants and toddlers. In fact, during model building a different

parameter-covariate correlation was identified when analysing a separate data set from infants and toddlers. The use of hierarchical modelling enables accurate characterisation of pharmacokinetic distributions and pharmacokinetic properties, but extrapolations based on such parameter estimates may have limited value. The covariate-parameter relationship identified in a given population by currently accepted maximum likelihood criteria for covariate model building (i.e., model parsimony) may not apply beyond the range of observations, causing under or overprediction of the parameter in the new population of interest. It appears that the use of goodness-of-fit to guide model building and validation acts as a long rather than a short stop. It prevents the incorporation of parameters and correlations which are not supported by the likelihood. This issue raises important concerns about the use of modelling, as extrapolations are often made from an older to a younger population (typically the case for paediatric drug development). In this case, a re-parameterisation of drug kinetics might be required to include changes caused by the developmental changes occurring in these subpopulations. The same covariate (i.e. body weight) may remain a surrogate for the scaling function in different subgroups, but its relationships with the pharmacokinetic parameters must be re-assessed in order to include, for example, differences in maturation.

Based on the aforementioned, it is clear that the estimation of covariate effects, which constitutes a critical step in the characterisation of the pharmacokinetic properties of a drug, does not necessarily guarantee accurate extrapolation of parameter distributions from a reference population to another population. In Chapter 6, we have expanded our evaluation of model performance by looking at the accuracy of interpolations obtained by model-based approach. Using a model built on a subset of pharmacokinetic data from infants, toddlers and adults, we have attempted to predict pharmacokinetics in children and adolescents. From a methodological point of view, interpolations and extrapolations assume the continuity of covariate-parameter correlations beyond the range of observations. In this case, the paradigm compound was midazolam, a short-acting imidazobenzodiazepine, used for inducing sedation and amnesia before medical procedures. Our analysis was challenged by another important conceptual issue: current knowledge of the ontogeny for CYP3A4 in infants and toddlers clearly prevents the use of common parameters distributions across populations. Hence, the introduction of parameter priors to support parameter estimation was not applicable. Moreover, the narrow range of body weight in the infant and toddler population and the gap between this group and adults prevented a thorough covariate analysis. We had to resort to allometric correlations between parameters and body weight. In a similar way to what we have described previously for abacavir extrapolations, the predicted concentration *vs.* time profiles and parameter distributions obtained by interpolation showed some discrepancies compared to the parameter distribution values observed from estimation procedures. The model built on infants, toddlers and adults data constantly underpredicted midazolam exposure in children and adolescents across the whole body weight range, with the underpredictions becoming larger with increasing body weight.

These findings corroborate our views that currently accepted tools for model

building based on maximum likelihood methods do not allow us to discriminate *descriptive* models from *predictive* models. A model that satisfies all standard diagnostics tests (goodness-of-fit, visual predictive check, normalised prediction distribution errors, mirror plots, etc) can be considered acceptable for its ability to accurately describe the data on which it was built. No matter how “mechanistic” the choices for parameterisation are, inferences about parameter distribution and parameter-covariate correlations beyond the observed data cannot be made without accounting for uncertainty. Simulations-based diagnostics (as NPDE and mirror plots) apparently should give indications on the predictive power of a model, but again the results of such tests are only valid if the simulated subjects belong to the same population as the observed one.

The discrimination between descriptive and predictive model is particularly crucial in paediatrics as sub-populations exist with major differences across the age span from 0 to 18 years. However, from a clinical perspective, it should be noted that building a different model for each subpopulation is obviously not an option or solution. A strategy is required that allows the assessment of differences in pharmacokinetics taking into account not only parameter but also model uncertainty. In part 3 of this thesis, a pragmatic approach was proposed for dose adjustment and dosing recommendations that may overcome the intrinsic limitations of maximum likelihood methods and inaccuracy of predictions by hierarchical pharmacokinetic models.

The somewhat unexpected findings have prompted our attention to evaluate the implications of another common practice in paediatric pharmacology, i.e., the use of drug combinations according to a fixed-dose ratio. This practice relies on the assumption that fixed-dose combinations yield comparable exposure in children and can therefore be considered as effective and safe as in adults. Another hidden assumption underlying such practice is that, whatever covariate has been identified for the scaling of the dose, parameter-covariate correlations do not only remain constant beyond the range of observed data, but also that the correlation remains exactly the same for both moieties. These views are challenged in Chapter 7, where we have assessed how to best provide dosing recommendations for the anti-malarial combination of atovaquone and proguanil. The current dosing regimen for the combination is based on body weight and the marketed product has a different dosage strength available for the paediatric indication. Yet, the ratio between the active moieties remains the same (2.5:1). Pharmacokinetic models were developed for the two compounds and simulations performed to establish dose recommendations, in a similar fashion to what has been previously done for abacavir.

The analysis of atovaquone and proguanil confirmed the relevance of a model-based approach to support dose bridging from adults to children. However, our analysis showed the implications of model uncertainty due to additional factors which may remain unaccounted for even after comprehensive model evaluation. Ethnicity was found to be as important as body weight in determining differences in pharmacokinetic profiles and therefore in determining the requirements for dose adjustment. Such differences cannot be predicted if the dose rationale is purely

based on the evidence from the tested covariates. In addition, the use of model-based approach demonstrated that the ratio between compounds should be treated as any other pharmacokinetic parameter and therefore adapted accordingly to the covariates that determine the overall exposure to the drugs in the combination. It should be underlined that atovaquone and proguanil remain a very effective and safe combination even with the fixed ratio, but this should not be generalised. Maintaining a fixed ratio irrespective of changes in parameter-covariate relationships does not guarantee the same benefit:risk ratio across different age groups in the population. An important consequence of this practice is that treatments may be considered unsafe or ineffective, whilst the problem may be simply due to the wrong dose of one or both moieties.

10.3 Protocol implementation and trial design factors in paediatric trials

The analysis of the four compounds presented in the previous section (abacavir, midazolam, atovaquone and proguanil) demonstrated that a model-based approach is required to support dose bridging from adults to children. At the same time, however, it shed light on the issue of prediction accuracy and uncertainty (i.e., model misspecification). Extrapolations to a new paediatric population cannot solely rely on the parameter-covariate correlations derived from the data available during model building. In other words, hierarchical modelling allows the identification of parameter distributions and consequently better characterisation of the factors explaining inter-individual variability, but current procedures supporting model building and validation do not address model uncertainty, which is critical for extrapolation and accurate predictions across populations.

Whilst accuracy and uncertainty may sound as a purely statistical rather than clinical issue, the errors or bias in dosing recommendation can ultimately have clinical implications, depending on the therapeutic window of the drug of interest. Unfortunately, there are no methodologies available to dismiss the so-called predictable risk. In fact, the implications of inaccuracy and uncertainty become evident when assessing a compound's liability for safety, toxicity or lack of efficacy during a *first-time-in-children* (FTIC) trial. In contrast to first-time-in-human trials in healthy subjects, dose escalation procedures are not permitted in children and the extrapolated dose from adults or from pre-clinical data must be as accurate as possible. Given that uncertainty about model and parameter distributions cannot be dismissed by statistical procedures, flexible protocol designs must be considered to allow accurate dose selection.

In the third section of this thesis we focused therefore on protocol designs that mitigate the impact of uncertainty about the right dose range in children. This strategy should facilitate the implementation of bridging concepts without compromising the actual outcome of the studies. The inclusion of adaptive procedures is proposed for paediatric protocols, which can specifically address the aforementioned

issues. Of particular interest is the use of randomised concentration-controlled trials (RCCT). Instead of randomising patients by dose level, as in the standard randomised dose-controlled trials (RDCT), in a RCCT patients are randomly assigned to treatment groups based on exposure or concentration ranges (or other measures of drug exposure). During the study, each patient's dose is adjusted to keep the patient within the pre-specified randomisation range. In theory, other than tackling uncertainty, this design enables considerable reduction in pharmacokinetic variability, allowing a better description of the concentration-response curve. In addition, these procedures can allegedly increase the statistical power of the study and therefore decrease the required sample size, as compared to standard RDCT.

Clinical trials simulations (CTS) were performed to evaluate the feasibility of our proposal and assess the implications of the adaptive procedures in a RCCT. The use of CTS allowed careful evaluation of a wide range of conditions and "what if" scenarios. In Chapter 8 an adaptive clinical trial was proposed for the evaluation of abacavir. In this case, we simulated a scenario in which a drug is not licensed for children, but already used off-label in the paediatric population. In other words, a situation where some information has already been collected in children and the purpose of the trial is primarily to confirm whether the dose clinically used is accurate, or to recommend a dose or dose range for which the benefit:risk ratio is higher. In this chapter we showed that the linear scaling of the dose according to body weight (as in the current paediatric dosing regimen) provides a mean exposure to abacavir comparable to the one observed in adults. However, the distribution of individual exposures was found to be more variable, with nearly half of the subjects remaining outside the target range of exposure that was deemed correct. In contrast, after adaptation of the individual doses, the median exposure remained similar to the target exposure, while the number of subjects within a sub-optimal range decreased 5-fold. It became clear that rather simple procedures for dose adaptation can minimise pharmacokinetic variability and consequently ensure drug exposure is comparable in adults and children. In addition, the application of the methodology to real data (i.e., the 14 children included in the original trial) demonstrated that adaptive procedures indeed allow shrinkage of the exposure distribution around the target range, irrespective of the study size. Overall, this means that fewer patients will potentially be under or overdosed during the course of treatment. Most importantly, these procedures ensure that dosing recommendations arising from a clinical trial are accurate and meet bridging requirements.

In contrast to the previous chapter, in Chapter 9 a FTIC trial was simulated for atovaquone and proguanil. In this case, the scope of the clinical trial simulations was to evaluate the implications of adaptive procedures for drug combinations under the assumption that none of the compounds had been previously used in children. The only information available refers to data from phase I and II trials in adults. The initial dose was extrapolated using a bridging strategy based on the modelling of adult data. Given the lack of information about the pharmacokinetics of the drug in children, various scenarios were considered that mimic different degrees of metabolic activity and maturation. Moreover, we showed how to handle

the effect of “unidentified” covariates. Our results indicate that it is possible to adapt the dose and minimise pharmacokinetic variability in FTIC trials.

Our findings also suggest that the proposed adaptive procedures can be implemented irrespective of the degree of uncertainty about the differences in pharmacokinetics between adults and children. Following dose adjustment, drug exposures were clustered around the target range even when pharmacokinetic parameters in children were very different from adults. In addition, special attention was paid to the assessment of covariate effects and differences in parameter-covariate correlations in the new population. As indicated previously, covariates that influence pharmacokinetics in children may not be detected in the analysis of adult data and vice-versa, leading to biased conclusions about the dosing regimen required for children. The use of a flexible protocol design with adaptive procedures, like a RCCT, limits the impact of model misspecifications or parameter uncertainty arising from pharmacokinetic data in adults.

10.4 Perspectives

We conclude this thesis raising the very initial question that triggered our research programme: does size matter? As provocative as it may sound, the myth of size has pervaded behaviour and beliefs in paediatric pharmacology. It has become a dogma in science, which takes size as surrogate for function, dismissing any consideration for the evidence that they are not necessarily correlated and often confounded by other determinants of drug response. The methodology proposed in this thesis for defining the dose rationale for children represents an attempt to break some of the most entrenched practices in paediatric pharmacology, e.g. the use of a linear correlation between dose and body weight, age or body surface.

We have showed the potential of a bridging approach and the benefits that such strategy can represent to the implementation of paediatric trials. Whilst we have generated evidence, demonstrating that size may not be assumed to linearly correlate with function and that in some cases size is by far less important than factors such as ethnicity, many aspects remain that require further understanding.

One of the most striking findings was the limited value of model-based extrapolations and of accepted validation procedures for predicting pharmacokinetics across populations. These limitations are reflected mathematically and statistically in terms of parameter accuracy and model uncertainty, some of which can be circumvented by the use of adaptive protocols. However, there is still much to learn about accuracy in parameter estimation methods and the relationships between parameter and covariates, two major causes of the imprecision in scaling and extrapolations.

First, one needs to consider that uncertainty will be a common denominator for therapeutic areas in drug development whenever new target and candidate molecules are selected to progress into clinical development. From a clinical and scientific perspective, parameterisation of the physiological processes associated with absorption, distribution, metabolism and excretion will have to be coupled to

the identification of influential factors by means of inferential methods. Additional complexities will need to be accounted for when dealing with topical delivery and biological and biopharmaceuticals, for which the role of systemic exposure is limited to safety aspects and pharmacokinetic properties are intertwined with pharmacodynamics.

Second, it must become clear that simulations play an equally important role in research, as modelling itself. Furthermore, the concept of modelling needs to be disentangled into two parts: models for estimation and models for simulation. Whilst much debate has been ongoing on the importance of identifying parameters, which should capture time variant physiological function and thereby discriminate between drug and system-specific properties, a critical aspect is being ignored, namely that the statistical method (and algorithms) ultimately determines the choices one makes about the model parameterisation and the parameter-covariate correlations.

Hence, we envisage that further research in paediatric pharmacology must endeavour the refinement of the methods for model acceptance, including procedures that would allow one to assess model performance beyond the range of data available for estimation. To this purpose, **goodness-of-fit** needs to be replaced by **goodness-of-prediction**, i.e., a different set of criteria independent from the the likelihood (data) evidence. Without such a refinement, paediatric pharmacology is likely to remain a prisoner in Plato's cave. In the fictional dialogue between Plato and Socrates, a group of people who have lived chained to the wall of a cave all of their lives face a blank wall. The people watch shadows projected on the wall by things passing in front of a fire behind them, and begin to ascribe forms to these shadows. According to this metaphoric figure, the shadows are as close as the prisoners get to viewing reality. Statistical methods are like the fire in the allegory of the cave, determining what we perceive as reality. Part of the challenge in unravelling substrates and subsequently parameterising physiological processes that accurately describe the changes due to developmental growth do not depend on scientific advancements but on the most fundamental kind of knowledge, i.e., the evolution of conceptual knowledge.

Given the availability of suitable methods, the reliability of extrapolations from simulations will also depend on the possible choices for parameterisation. It should be clear that the use of demographic covariates to describe differences in pharmacokinetics may not solve the issue of accuracy and uncertainty. From a clinical perspective, it is understandable that dosing algorithms should remain as simple as possible, irrespective of the magnitude of changes in pharmacokinetics. In this sense, the use of demographic characteristics as the basis for dosing recommendations seem to mitigate the impact of prescription errors and other human-related mistakes, which are more likely to occur otherwise.

One potential solution to this problem will require changes in protocol design and better integration of *in vitro* and *in vivo* data, including additional protocol measurements to allow the assessment of factors which are more closely related to the changes in physiological function during developmental growth. For example, changes in clearance can be parameterised in terms of enzymatic ontogeny and

metabolic capacity rather than by surrogate measures as body weight. The use of metabolic probes *in vivo* could also be considered in conjunction with evidence from *in vitro* data. This approach would be similar to currently accepted procedures for evaluating liability to drug-drug interactions. This type of data can then be analysed by physiologically based PK (PBPK) modelling [5]. In contrast with classical compartmental pharmacokinetic analysis, PBPK models are usually multi-compartment models, where the compartments correspond to organs or tissues. PBPK models include anatomical, physiological and physicochemical properties in the description of the pharmacokinetics, striving to be as mechanistic as possible. Given their mechanistic properties, PBPK models may be better suited for prediction and extrapolations if used together with novel statistical methods. This transition from descriptive towards mechanistic modelling proved to be a valuable tool in translational drug research. A key feature of this mechanism-based approach is the explicit distinction between drug-specific properties and biological system-specific properties [6]. Drug-specific parameters describe the interaction between the drug and the biological system in terms of target affinity and target activation, whereas system-specific parameters describe the functioning of the biological system [7]. This distinction would also be crucial to accurately predict the properties of drugs in paediatric populations, but so far, little has been done to incorporate system-specific characteristics for dose extrapolation purposes. To date, differences in metabolic maturation, solubility and permeability limited-absorption, body fluid composition, etc. are not parameterised as time-variant processes. *In vitro* - *in vivo* (IVIV) correlations are required to describe how enzymatic activity, maturation and capacity changes with age (time) and organ function. In theory, one could use probe compounds to correlate the activity *in vitro* with different stages of enzymatic ontogeny and therefore simulate the impact that maturation can have on clearance and metabolism [8]. However, these concepts are far less evolved for large molecules, for which hepatic metabolism is relatively small compared to the role of tissue catabolism (i.e., target-mediated drug disposition). Similar considerations apply to drug absorption and tissue distribution when developing novel compounds for topical delivery. *In vitro* - *in vivo* correlations and between-species differences have not been characterised sufficiently well to allow further investigation of the role of developmental growth in humans and its impact on exposure and target engagement.

It can be anticipated that the availability of PBPK or equivalent mechanism-based models may partly address our plea for the need to perform scaling for function when defining the rationale for paediatric doses. In a model-based framework, the identification of different descriptors of the changes occurring across the paediatric subpopulations or between children and adults does not preclude further evaluation of how dose adjustment based on a surrogate of size would perform in clinical practice as label recommendations. The differences between the aforementioned approach and current practice are not trivial. No pre-defined relationship is imposed between pharmacokinetics and demographic characteristics and simulations scenarios based on parametric distributions are used to account for the implications of inter-individual variability, neither of which is currently applied

in early development.

Irrespective of the choices for model parameterisation, the limitations imposed by parsimony principles and maximum likelihood estimation (MLE) methods cannot be neglected when scaling for function. According to MLE principles, the algorithm selects values of the model parameters that produce a distribution that gives the observed data the greatest probability. In this way, there is (and there will always be) a very strong connection between models and data. Simply, MLE does not allow for model parameters and correlations to be included if evidence is not present in the data. A more suitable approach to tackle paediatric research in early clinical development involves the introduction of more comprehensive Bayesian methods. In this thesis, we have showed a few elements of Bayesian modelling as an alternative to traditional covariate model building (Chapters 4 and 6), but estimation procedures remained within a MLE framework. As indicated above, goodness-of-prediction measures are required to ensure model and parameter selection for extrapolation purpose. Hence, a modelling approach is envisaged that is not based on parsimony, allowing the ranking of multiple models and parameter-covariate correlations in order of probability. In this way, the choice of one model or another will rely on data as much as on prior knowledge available at the moment of the analysis [9]. Bayesian Model Averaging (BMA) has evolved as a technique designed to account for the uncertainty inherent in the model selection process, something which traditional statistical analysis often disregards. By averaging over many different competing models, BMA incorporates model uncertainty into conclusions about parameters and prediction. BMA has been applied successfully to many statistical model classes including linear regression, generalised linear models, Cox regression models, and discrete graphical models, in all cases improving predictive performance [10]. Unfortunately, despite successful implementation in epidemiology [11], econometrics [12], chemistry [13] and even weather forecast [14], its dissemination into pharmacology and pharmacokinetics remains extremely limited [15].

In summary, does size matter for dose selection in paediatric indications? Definitely yes, but only when size is a surrogate for the differences in physiological function associated with developmental growth. Given the role of disease and many other clinically relevant factors known to affect pharmacokinetics and pharmacodynamics in children, the assumption of a pre-defined correlation between size and function cannot be taken for granted.

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