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Modelling & Simulation as a Research Tool in Paediatric Drug Development

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ABSTRACT

Although practical and ethical constraints impose special requirements for the evaluation of treatment safety and efficacy in the paediatric population, the main issue remains the empirical basis for patient stratification and dose selection at the early stage of the development of new chemical and biological entities.

Modelling and simulation (M&S) enables the assessment of the impact of different regimens as well as of different populations on a drug's safety and efficacy profile. It has been widely used in the last two decades to support pre-clinical and early clinical drug development. In fact, M&S has been applied to drug development as a decision tool, as a study optimisation tool and as a data analysis tool. In particular, this approach can be support dose adjustment in specific subgroups of a population. M&S may therefore allow the individualisation of drug therapy, improving the risk benefit ratio in children.

The lack of consensus on how to assess the impact of developmental factors on pharmacokinetics, pharmacodynamics and safety has prevented so far a broader use of the approach. This problem is compounded by the limited collaboration between stakeholders, which prevents data sharing in this field. In this article we emphasise the need for a concerted effort to promote effective use of this technology in paediatric drug development and avoid unnecessary exposure of children to clinical trials.

1 INTRODUCTION

Model-based drug development represents an invaluable resource in pharmaceutical R&D¹. The recent introduction of regulatory requirements for the development of medicines for children will have far reaching impact on how evidence can be generated on the risk-benefit on novel treatments for paediatric diseases. These requirements make the application of model-based approaches an obligatory step in paediatric drug development. In his paper we show how modelling & simulation (M&S) has been applied to drug development as a decision tool, as a study optimisation tool and as a data analysis tool. These applications are split into three main sections, with special focus on how these different domains can support drug discovery, nonclinical and clinical development. In addition to the role of mechanistic models that are surfacing from research in systems biology and systems pharmacology and their contribution to the rationale for patient selection and paediatric dosing regimen, practical and ethical limitations imposed by empirical protocols are highlighted. The landscape is then completed with an overview of the implications of M&S for the advancement of the concept of personalised medicines in children. Ultimately, this manuscript attempts to emphasise the need for less empirical evidence and for a more systematic, integrated evaluation of overall risk benefit ratio of novel treatments in children.

1.1 Systems Biology and Systems Pharmacology

The use of computer-aided mathematical simulations to describe biological processes and systems is a fundamental part of systems biology². The objective of such simulations is model-based prediction of the behaviour and the dynamics of biological systems. In this manuscript, focus is given to the role of modelling and simulation (M&S) in systems pharmacology and paediatric diseases. In this context, models can be used to quantitatively characterise how drug effects affect the dynamics of biological systems as well as the regulatory mechanisms triggered by a given pharmacological intervention³.

Because of the complexity of biological systems simplified models are often used^{4;5}. However the quality of model-based predictions strongly depends on the quality of the model which in turn is defined by the quality of the data and the profoundness of the knowledge it is based on. Whilst simplified models have been particularly useful for interpreting clinical data and developing novel biomarkers, complex models may be required to predict the overall clinical response or to quantify the role of modulating individual pathways or targets in health and disease conditions.

These requirements have resulted into two different approaches in the evaluation of the dynamics of biological systems, namely a “bottom-up” and a “top-down” approach. The “bottom-up” approach, historically used by biologists, brings together all the known pieces at a subsystem level with the objective of identifying a formal structure of the whole system; a clear drawback is that it doesn’t account for possible unknown factors. In contrast, the “top-down” approach departs from an observable and clinically relevant behaviour and then iteratively identifies the biological components which could yield or cause such behaviour. Both methods are complementary and have a wide range of applications⁶⁻⁹. Despite the differences in the focus of each approach, over the last few years, has become clear that to fully understand the complexity of biological organisms they must be studied as whole systems; the “top down” approach seems to satisfy this requirement².

The use of M&S in drug development has allowed the advancement of translational research, allowing analysis of complex biological systems and their interactions with chemical and biological entities (i.e., drugs and biologics). This field has evolved into what is currently defined as systems pharmacology. In conjunction with additional statistical concepts, M&S has become a powerful tool for predicting drug effects across a wide range of conditions, including extrapolation from *in vitro* to *in vivo*, from animal to humans, from health to disease, from short to long-term effects.

Despite the increase in the use of M&S as tool for decision-making in pharmaceutical R&D, its benefit as optimisation and data analysis tool has remained undervalued and sometimes ignored by key stakeholders^{10;11}. This attitude appears contradictory to ethical and scientific tenets which should underpin the evaluation of risk-benefit ratio in special populations, such as paediatrics. The ethical constraints and practical limitations associated with clinical research clearly impose new alternative methodology to ensure accurate assessment of treatment response in these patients. In that sense, the value of M&S to the paediatric research may be even greater than the evidence available so far for drug development in adults. The interest towards M&S is also reaching the attention of regulatory authorities. In April 2008, the European Medicines Agency (EMA) organised a “Workshop on Modelling in Paediatric Medicines”¹². More recently, M&S has been proposed as a framework for the evaluation of drugs by regulators taking into account different clinical scenarios^{7;13}.

1.2 Clinical research in paediatric diseases

As indicated previously, the purpose of the manuscript is to evaluate the use of M&S as an alternative approach for the design, analysis and interpretation of experiments and clinical protocols in paediatric drug development. Despite some limitations, M&S enables systematic, integrated evaluation of drug and disease properties, providing quantitative measures of treatment response across a wide range of clinical and statistical designs, some of which would not be feasible in real-life (i.e., due to exclusion criteria). M&S can overcome many of the pitfalls associated with the use of empirical protocols and isolated, sequential developability criteria.

It should be noted that in spite of the ICH E11’s explicit requirement for appropriate evaluation of medicinal products for children, today about 70% of the medicines given to the paediatric population and 93% of the medicines given to critically ill neonates remain unlicensed or used off-label¹⁴⁻¹⁶. One of the greatest challenges in paediatric drug research is to find the appropriate dosing regimen.

Even if a large number of studies have been performed in paediatrics in the last decades, the empiricism upon which clinical drug development is based, often results in ineffective or unsafe treatments. To ensure that appropriate dose rationale and dosing regimens are used in paediatric trials, as well as to identify potential subgroups of patients who may be more susceptible to treatment response and/or adverse events, it is essential to characterise the underlying pharmacokinetic-pharmacodynamic (PKPD) relationships¹⁷. PK and PD properties may change in children over the whole age continuum, and these changes must be considered, especially when interpreting nonclinical safety pharmacology and toxicology data^{14;17-19}.

Understanding the effects of medicinal products in paediatric patients is an important goal. However, this should be done without compromising the well-being of paediatric patients participating in clinical studies. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole²⁰. It is clear that traditional drug development approaches do not satisfy the aforementioned requirement. In contrast, M&S can be used to address various practical, scientific and ethical issues which arise in paediatric research.

2 EMPIRICISM IN PAEDIATRIC DRUG DEVELOPMENT

The majority of drugs on the market have been developed primarily for adults²¹. Several constraints have been used to justify the poor assessment of efficacy and safety in the paediatric population, and consequently provide appropriate labelling recommendations for children. These constraints can be categorised into three classes, namely: practical, ethical and regulatory.

Practical issues are principally the increasing cost of clinical development and the availability of patients required to satisfy the statistical power of each study²² (e.g., these criteria cannot be applied to paediatric patients with rare diseases). Patient autonomy and unforeseen adverse events represent some of the ethical factors which limit the application of empirical experimental design in paediatric

drug research^{15;23}. These limitations constrain physicians to extrapolate data from the adult population and to normalise dosing regimens to a child's body weight or body surface area without evidence of linear correlations for the changes in the parameters of interest across populations (see examples in Table 1)^{16;24}.

The FDA's paediatric study decision tree is very clear in recommending bridging and dose selection from adults to children, and its purpose is to streamline cost and time required to develop drugs in the paediatric population²¹. The bridging rationale, and as such the data extrapolation, can be justified only if the following conditions are all met. Adults and children have to present 1) the same disease progression; 2) similar PKPD relationships; and 3) similar endpoints. If these requirements are not met, further PKPD or efficacy studies are needed. We anticipate that M&S methodology can result in important improvement in planning, implementation and analysis of such studies⁷. In fact, the ICH E11 already proposes the use of population PK analysis in paediatric studies in order to facilitate the study and to reduce practical and ethical constraints²⁰.

From a regulatory perspective, lack of working knowledge and understanding of M&S concepts create an additional hurdle to the effective use and implementation of the approach in regulatory submissions. Despite the opportunities for the use of M&S by regulatory guidelines, empiricism still plays a main role in drug development. As recently shown, a keyword-based search performed on 95 European Public Assessment Reports (1995 – 2007) reveals that only 22 out of the 95 documents analysed refer to the use of M&S methodologies. Furthermore, these EPARS do not include keywords such as biosimulation, PKPD modelling or clinical trial simulation.

3 MODELLING & SIMULATION

In addition to the insight into the underlying pharmacological mechanisms and dynamics of a biological system, M&S also enables the assessment of important statistical elements. These integration of these elements is currently known as

pharmacometrics. In pharmacometric research, three important components are characterised, namely: a drug model, a disease/placebo model and the implementation model (trial design and decision criteria). Whilst modelling enables translation of relevant features of a system into mathematical language (i.e., model parameters), simulation allows the assessment of a system's performance under hypothetical and real-life scenarios (i.e., "what-if" scenarios), yielding information about the implications of different experimental designs and quantitative predictions about treatment outcome, dosing requirements and covariate effects (Figure 1)^{7;24}.

In this regard, the great advantage of the use of M&S in paediatric drug development is the possibility to explore relevant scenarios before enrolling children into a clinical protocol. Simulations allow evaluation of a range of parameter values (dose, clearance, etc.), including an assessment of critical scenarios, such as overdosing, that cannot be generated in real-life studies¹⁵. Most importantly, it enables systematic assessment of the impact of uncertainty.

M&S can be used not only as a learning and decision-making tool, but also as a design optimisation and data analysis tool. Consequently, it can support the selection of candidate drugs and streamline decisions regarding first-time in human, PKPD and safety/efficacy clinical studies^{7;24;25}. Furthermore, great attention is being paid to study design before the implementation of an experiment or clinical protocol. In brief, M&S can be applied to the development of a new drug from the first steps in discovery to the approval stage. Later in therapeutics and clinical practice, M&S can guide dose adjustment for specific subgroups of a population and to explore the implications of clinical factors, such as treatment adherence, changes in formulation and drug combinations^{22;26}.

Like all sciences, best practices should be followed when performing M&S. To fulfil this objective the following issues must be clearly defined a priori: 1) the objective(s) of the M&S exercise; 2) the criteria for data selection and the exclusions or limitations of the dataset; 3) assumptions and rationale for model

selection or simulation features; 4) the statistical method, algorithm and methodology; and 5) model qualification criteria. It should be noted that the workflow and tools should have an audit trail and be validated to ensure reproducibility of the findings^{7;26}. The advantages and drawbacks of model-based approaches from drug discovery to the clinical practice will be highlighted in the following paragraphs.

3.1 M&S in drug discovery

During lead optimisation and candidate selection go/no-go decisions have to be made. From the very first step of development of an NME, ADME information is required to understand drug's properties *in vivo*^{27;28}. The application of M&S methodologies at this stage will support and facilitate decision-making processes. Predictive models assist the selection of appropriate candidates, as well as the design of *in vivo* PK studies²⁹. The obvious advantage of this application is the possibility to integrate *in vitro* to *in vivo* properties as well as to pharmacodynamic characteristics, identifying differences in drug performance *in vivo* as compared to decision-making based on isolated developability criteria. This concept has been recently applied in the evaluation of COX2 inhibitors³⁰. Furthermore, M&S allows optimisation of experimental protocols.

At this stage, pharmacokinetics can also be evaluated by studying each part of the ADME process in an integrated manner. Physiologically-based pharmacokinetic (PBPK) models provide an integrated view of drug disposition *in vivo*²⁷. In contrast to empirical compartmental models, a PBPK model aims at describing the *in vivo* behaviour of the drug before the acquisition of *in vivo* data. PBPK relies primarily on describing drug disposition in terms of organ distribution, blood flow and metabolic capacity (Figure 2). This allows better understanding of PK properties, more rational candidate selection, and extrapolation of dose levels, of routes of administration, and of data across species. This approach has some appealing features in that predictions can be made about the need for changes in dosing regimen due developmental and other age related factors^{7;27;29}.

The relevance of this type of information is evident already at lead optimisation stage: better and quicker understanding of a drug's PK profile *in vivo* may drastically improve decision making processes. Nevertheless, it is worth to highlight that the predictive value of these models depends on the selection of right model parameterisation and on the availability of suitable descriptors (i.e., experimental data reflecting the appropriate set of physicochemical properties)²⁸.

3.2 M&S in nonclinical drug development

At the nonclinical phase *in vitro* and *in vivo* animal studies are the main source of information about pharmacokinetic and pharmacodynamic properties. The objective at this stage is to further improve the understanding of the drug properties *in vivo* and to extrapolate findings, identifying correlations or making predictions about a drug's performance in humans (i.e., clinical response).

Juvenile toxicological studies, which involve young animals have been used to investigate drug's pharmacology and toxicology. Findings are extrapolated assuming a correlation between developmental growth in animals and children³¹. Even if the assumptions and rationale can be supported for some indications, numerous issues have to be addressed to allow appropriate interpretation of the findings. The use of M&S can optimise the use and interpretation of those data enabling a mechanism-based, systematic extrapolation of the data across species (e.g. scaling exposure findings for differences in metabolic clearance). Furthermore, it allows quantitative assessment of age or growth-related differences in drug effects and consequently the potential implications for different paediatric age groups^{18;21}.

Furthermore the techniques available at this stage, PBPK and PBPK-PD models²⁵, can use *in vitro* data to predict plasma and tissue concentrations³². This implies substantial reduction in the number of animals per experiment and sometimes the replacement of animal by *in silico* experiments. It should be

highlighted that a model-based approach allows optimisation of experimental protocols, improving the accuracy and efficiency of data extrapolation.

In summary, the benefits from M&S methodologies at the non-clinical stage include the prediction and characterisation of primary PK parameters (PBPK models) and pharmacodynamic properties (PBPK-PD models). Model parameters can then be used to predict the dose range to be tested in clinical studies, including the requirements for optimal sampling and study design^{7;25;26}.

3.3 M&S in clinical drug development

Limited availability of patients and practical constraints, such as difficulties, in blood sampling, have often been used as justification to the lack of systematic evaluation of drug response in children¹⁴⁻¹⁶. M&S could address many of these limitations, but its wide implementation in clinical development has remained wishful thinking. This is partly due to the lack of understanding and working knowledge in quantitative pharmacology and pharmacometrics by sponsors, regulatory agencies and investigators (e.g., paediatricians, statisticians, research nurses) who are responsible for the planning, design and/or approval of clinical trials.

3.3.1 PBPK and disease models

The difficulties in performing paediatric trials constrain physicians to extrapolate data from the adult population to children. For this purpose, simple allometric methods based on body weight or body surface area have been frequently used. However, particularly in neonates and infants, the use of the allometric approach may fail in identifying the appropriate dosing range^{16;21}. Once more PBPK models may play a pivotal role in the estimation of dosing requirements across the paediatric population. Physiological differences between adults and children and between different age groups can be incorporated in the model to evaluate variation in pharmacokinetics. This may allow conversion of the exploratory nature of first-in children studies into a confirmatory step²¹.

Application of bridging techniques requires however further understanding of disease. Therefore, disease and disease-progression models need to be considered when comparing drug response and kinetics between adults to children⁷. Disease models can also be applied to simulate treatment response. In combination with drug models, it is possible to explore the implications of different algorithms for dose adjustment⁷. The use of disease models to evaluate drug-disease interactions and the role of covariates on pharmacokinetics, pharmacodynamics and treatment outcome demand the use of somewhat sophisticated statistical methods, which cannot be achieved by standard linear regression techniques. These methods often rely upon Bayesian statistical concepts and include parameterisation based on hierarchical, nonlinear mixed effects models, also known as population approach.

3.3.2 Population models

Population methods consider the population rather than the individual as the object of the investigation. The approach is particularly suitable when information on individual subjects is limited (i.e., sparse sampling). In fact, this is a common situation in pharmacokinetic and pharmacodynamic studies in children. Hence, it would be already possible to circumvent the aforementioned practical and ethical issues in paediatric research^{14;33}. It is unfortunate that the expertise is still limited to allow its widespread use in drug development. Conceptually, population models rely on pooled data across treatment cohorts or even across different studies¹⁵, which is of great importance considering that the number of paediatric patients in some diseases may be extremely limited. Moreover, one can evaluate different clinical scenarios without exposing children to any risk, and explore drug, disease or covariate effects in a larger number of virtual patients compared to what is observed in the patients enrolled in a real trial^{15;34}. A further advantage is the possibility to assess the clinical relevance of covariates on drug exposure and to evaluate simultaneously their effect on the treatment response³³. As an example, Knibbe et al. recently reported a population pharmacokinetic model to describe propofol disposition in children aged 1 to 5 years. In contrast to what

happens in adults, the model showed the body weight as a covariate for clearance³⁵.

Population pharmacokinetic (pop PK) and pharmacokinetic-pharmacodynamic (pop PKPD) models basically comprise the representation of three main components: a structural model which describes pharmacokinetics or pharmacodynamic characteristics (e.g., 2-compartment disposition, sigmoid Emax); a statistical model describing between-subject and an error model which accounts for the residual variability. Most importantly, population models incorporate the effect of influential covariates (e.g., weight, age, pharmacogenetics, etc.)^{7;14;15} on model parameters (e.g., CL, EC50), rather correlating them directly to the observed variables. This is particularly appealing, as it prevents the bias common to empirical methods aimed at the assessment of covariate effects in the presence of non-linear pharmacokinetics and complex PKPD relationships²⁶. This concept is clearly illustrated by Ihmsen et al, who applied a PKPD model to characterise the delayed onset and prolonged recovery of rocuronium. The authors show the impact of disease on drug potency when comparing healthy subjects to patients affected by Duchenne muscular dystrophy³⁶.

Another concept introduced into paediatric research is KPD models. They represent a specific group of nonlinear mixed effect models, which has been developed to describe exposure-effect relationships in the absence of drug concentration measurements^{7;37}. This approach is very useful if drug elimination from the biophase is the rate-limiting step in drug disposition³⁷. The approach is however not suitable for extrapolating data across different scenarios (e.g. different doses, or populations) for which no observations are available⁷.

The availability of population PK and PKPD models offers an important opportunity as a study optimisation tool (e.g., dose selection, sampling times, treatment duration and population size). These models can also be used to support prediction and extrapolation of data across different age-groups, dosing

regimens and formulations or delivery forms (Figure 3)^{7;14;25;26;38}. Moreover, population models may enable extrapolation of long-term efficacy and safety based on short-term pharmacokinetic and treatment response data.

3.3.3 M&S and biomarkers

A biological marker or biomarker is defined a characteristic that is objectively measured and evaluated as an indicator of normal biologic or pathogenic processes or pharmacological responses to a therapeutic intervention^{30;39}. Biomarkers can be directly measured or derived by model-based approaches and expressed as model parameters. In drug discovery and drug development a validated biomarker may facilitate decision-making, supporting the prediction of treatment response as well as guide dose adjustment. If validated accordingly for sensitivity, specificity and clinical relevance, biomarkers can also be used as a surrogate endpoints (symptom or sign that constitutes one of the target outcomes). In this context, model-based analysis of biomarker data can contribute to validation procedures and enable comprehensive sensitivity analysis, with clear understanding of sensitivity and specificity rates (i.e., false positive and false negative). The availability of biomarkers may be determinant for the progression of a clinical trial when the clinical outcome is delayed or difficult to quantify in short term studies^{30;39}.

Another important advantage of model-based approaches is that they allow access to functional components and structures of a biological system which cannot be identified experimentally. The best example of such a concept is the quantification of insulin sensitivity, as defined by the insulin sensitivity index. The loss in insulin sensitivity due to diabetes progression cannot be measured direct from insulin and glucose levels in plasma; it is derived from a model. In addition, modelling and simulation provides insight into how drug treatments may alter disease^{40;41}.

3.3.4 Clinical trial simulation

In contrast to meta-analysis, clinical trial simulation (CTS) allows for the investigation of the impact of a range of design characteristics on the power to detect a treatment effect prior to exposing patients to an experimental drug. In a field where most clinical trials have a conservative design, this methodology offers a unique opportunity to evaluate innovative designs. Rather than performing power calculations which only take sample size and endpoint variability into account, CTS allows calculation of power taking into account a multitude of other factors.

In general, CTS utilises two types of models⁴². First, a drug-action (PKPD) model is considered, which comprises pharmacokinetic and pharmacodynamic factors. In chronic diseases the model also accounts for disease progression. Unfortunately, the lack of knowledge about the mechanisms underlying treatment response in many therapeutic indications has prevented the development of mechanistic PKPD models. Hence, examples often refer to standard statistical models, such as e.g., the mixed model for repeated measures (MMRM). Such statistical models have however a downside in that they often do not incorporate concentration-effect relationships and therefore do not allow for inferences about age-related differences in pharmacokinetics, as is the case for paediatric populations. Secondly, CTS requires a trial execution model. These models simulate other important aspects of the trial, such as dropout, compliance and protocol deviations (Figure 4). Thereby, one can determine all possible outcomes under candidate trial designs, allowing such trial designs to be compared in a strictly quantitative manner. Thus far, very few examples exist in which relevant design factors have been evaluated prospectively as part of the planning of a paediatric trial.

It is also important to stress that CTS allows investigation of factors that cannot be scrutinised by meta-analysis or empirical design. First, designs which have not been implemented cannot be included in a meta-analysis. Second, it is difficult to separate the influence of multiple design factors, whereas CTS allows evaluation of a single factor at a time. Although meta-analyses may provide

valuable information about differences in patient populations and treatment response, it is unfortunate that many investigators consider overall publication review sufficient to gather evidence on the role of design factors, as often suggested in the discussion of meta-analysis results.

If simulated data is to be exchangeable with actual patient data, it is imperative that not only model parameters are unbiased, but that estimates of variability are also accurate. Often interpretation of statistical model results focuses on the predicted values of the treatment effect. This does not necessarily mean that response distributions reflect what occurs in the true patient population. In fact, it is not infrequent to see model misspecifications being corrected by inflated estimates of variability. It is therefore critical for clinicians to understand that standard goodness-of-fit criteria do not take simulation characteristics into account and may therefore not be indicative of the best model. Such a comparison between simulated and original data can be performed using graphical and statistical tools.

CTS relies on the availability of accurate model parameter and corresponding distributions to investigate “what if” scenarios across a different range of conditions or design features, such as population size, stratification levels, dose range, sampling scheme, and even different endpoints. One of the main advantages of such a virtual or statistical experiment is the possibility to predict ‘trial performance’ and so to identify potential limitations in study and protocol design prior to its implementation^{7;24;43;44}. In fact, some clinical trial simulations have been evaluated against outcomes from real trials. They showed accuracy and an important correspondence between simulated and “real” results²⁶. For instance, Nguyen et al. have developed a new dosing regimen for busulfan in infants, children and adolescents through the use of population PK model. The new regimen has been accepted and adopted as conditioning treatment prior to haematopoietic stem-cell transplantation in paediatric patients since 2005⁴⁵. Another example of rational drug dosage is evident in the study from Laer *et al.* where population PK modelling and simulations have been applied to develop

age-based dosing regimens for sotalol in children with supraventricular tachycardia. For children < 6 years the identified dose was higher than the one for neonates and children > 6 years⁴⁶.

3.4 M&S and personalised medicines

CTS represents one of the most obvious methods to explore the concept of personalised medicine and its implications in clinical practice. M&S techniques can be applied to identify patient subgroups and tailor dosing regimen for specific subsets of the population^{14;22}. PBPK-PD models, pop PK and pop PK-PD models, as well as disease models can all be used for this purpose^{7;18;21;26;47}. The use of a model-based approach for personalised medicines also permits better scrutiny of diagnostic and prognostic factors, including quantitative estimates of differences in the risk-benefit ratio for a given group of patients or treatment option. Despite the natural role of CTS in this field, so far its use has been relatively limited. Very few examples exist in which personalisation of treatment has been based on clinical relevance, rather than on pure scientific rationale. Recently, Albers et al used simulations to assess the implications of a new age-based dosing strategy for carvedilol. The study showed that higher doses in younger patients (with respect to body weight) are needed to achieve the same exposure as adults⁴⁸. Likewise, CTS has been used for diclofenac as basis for the evaluation of an effective and safe dosing regimen for acute pain in children⁴⁹.

Albeit a constant theme in scientific and regulatory forums, the use of personalised medicines concepts in paediatric indications remains wishful thinking. Both the FDA and the European regulatory authorities are increasingly requesting risk-benefit analyses of medicines. However, such appeals are not accompanied by suggested methods to be used in these analyses⁵⁰. Furthermore, it has not become clear to most stakeholders that empirical methods are not suitable for the evaluation of multiple risk and benefit criteria, in particular in the presence of potential uncertainty because of the incompleteness

of the evidence. Moreover, experimental evidence does not allow accurate assessment of the trade-offs of the benefits against the risks.

It can be anticipated that empirical evaluation of so many interacting factors cannot be defended without serious ethical and scientific issues. M&S techniques are a critical enabler for the implementation of personalised medicines and quantitative assessment of risk-benefit ratio at the individual and patient population levels. The use of a therapeutic utility index (TUI) illustrates such an endeavour. The concept has been introduced to enable the assessment of safety/efficacy of a treatment as a function of exposure. Using a model-based approach Leil *et al.* show that renal impairment has no impact on efficacy/safety despite significant differences in drug exposure⁵¹.

4 CONCLUSIONS

The recent changes in the legislation regarding paediatric indications and the increasing understanding in the mechanisms of paediatric diseases has created an unprecedented demand for evidence of the therapeutic benefit of new treatments in children. Such evidence cannot continue to be generated by empirical methods. There are simply not enough patients around to support drug development and approval processes in the same way one currently handles them for adult indications. Moreover, even if availability of patients were not an issue, practical and ethical aspects cannot be overlooked.

M&S can be used as a research tool to provide answers regarding the efficacy and safety of new drugs, in particular for paediatric and rare diseases. Despite some technical challenges, its potential value in paediatric research is indisputable and becomes greater as more data are accumulated through a development program. From a clinical and regulatory perspective, optimal use of M&S may lead to fewer study failures and smaller number of studies needed for generating the evidence required for the purposes of registration. As indicated previously, regulatory authorities have turned their interest towards the

application of M&S. However, to achieve the appropriate use of medicines in children (reducing burden of clinical trials and improving efficacy and safety of therapeutic treatments in this population) guidelines should be implemented to recommend the proper use of M&S techniques.

In conclusion, we have shown that M&S is a valuable tool to integrate and quantify the interaction between drug, disease and trial design factors. Such clear cut results cannot be obtained by traditional, empirical research protocols. Although M&S continues to play a supportive role to the design of empirical clinical trials. It can be anticipated that, in the future, model-based approaches will become both instrument and aim of drug development programs, yielding quantitative evidence of a positive risk-benefit ratio for a given population or dosing regimen without the burden of trial and error.

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52. LEGENDS FOR TABLES AND FIGURES:

Table 1. Examples of drugs commonly used in paediatric medicine for which the paediatric dose is not linearly correlated with body weight. Details about the clinical implication of nonlinearity between drug exposure and descriptors of body size can be found in Cella *et al.*, 2010.

Figure 1. Simulations allow the assessment of a system's performance under hypothetical and real-life scenarios (i.e., "what-if" scenarios), yielding information about the implications of different experimental designs and quantitative predictions about treatment outcome. In this example a model of haematopoiesis is used to simulate the effects of darbepoetin alfa administered every 2 weeks in chemotherapy-induced anaemia based on weight-based fixed-dosing regimens.

Figure 2. Physiologically-based pharmacokinetic (PBPK) models provide an integrated view of drug disposition *in vivo*. In contrast to empirical compartmental models, a PBPK model aims at describing the *in vivo* behaviour of the drug before the acquisition of *in vivo* data. PBPK relies primarily on describing drug disposition in terms of organ distribution, blood flow and metabolic capacity. Actual experiments become confirmatory and can therefore be optimised in terms of e.g., dose range, sample size, frequency and sampling intervals.

Figure 3. Modelling and simulation can be used to support prediction and extrapolation of data in early clinical development. The graphs show the implications of pharmacokinetic differences on systemic exposure across different age-groups in children. Based on pharmacokinetic parameter estimates systemic exposure can be simulated for a range of dosing regimens. Lines depict the fraction of patients categorised by body weight reaching target exposure criteria (A = AUC > 6.02 mg*h/L, B = plasma concentrations above IC₈₀ for at least 3 hours) following different doses of abacavir. o = 10 kg, † = 20 kg, ▲ = 30 kg, □ = 40 kg.

Figure 4. The diagram depicts the major components of a clinical trial simulation (CTS). In model-based drug development, CTS can be used to characterise the interactions between drug and disease, enabling among other things the assessment of disease modifying effects, dose selection and covariate effects (e.g., age, body weight). In conjunction with a trial model, CTS allows the evaluation of such interactions taking into account uncertainty and trial design factors, including the implications of different statistical methods for the analysis of the data.

Figure 5. The concept of personalised medicines implies quantitative assessment of risk-benefit ratio at the individual and patient population levels. M&S techniques are critical for such an evaluation. The use of a therapeutic utility index (TUI) illustrates how the safety-efficacy ratio of a treatment can be correlated to drug exposure. The graphs show (a) Safety: probability of a major or minor bleeding event as a function of daily steady-state apixaban exposure (AUC_{ss}). (b) Efficacy: probability of a venous thromboembolic event (VTE) as a function of daily apixaban AUC_{ss} and regimen. The shaded regions surrounding the regression lines represent the 90% bootstrap confidence intervals. The boxes at the bottom of each figure represent the distribution of apixaban exposures for the doses indicated. Exposure distributions are shown for total daily dose (TDD) because the distributions of AUC_{ss} should be the same for b.i.d. and q.d. regimens for the same total daily dose. Subjects with moderate renal impairment are expected to have a 43% increase in apixaban exposure; however, apixaban's therapeutic utility index suggests that dose adjustment is not needed in these subjects with renal impairment.

Table 1.

Drug	Therapeutic indication	Adult dose	Paediatric dose
Chloramphenicol	Bacterial infection	50 mg/kg/day	50 mg/kg/day neonates: 25 mg/kg/day
Carbamazepine	Epilepsy	5-8 mg/kg every 12 h	> 12 years: 5-8 mg/kg every 12 h Children: 3-10 mg/kg every 8 h Infants: 3-10 mg/kg every 8 h
Phenytoin	Epilepsy	2 mg/kg every 12 h	Children: 2.3-2.6 mg/kg every 8 h Infants: 2.3 mg/kg every 8 h Neonates: 2.5-4.0 mg/kg every 12 h
Propofol	Anesthesia	< 55 years: 6-12 mg/kg/h > 55 years: 3-6 mg/kg/h	2 months – 16 years: 7.5-18 mg/kg/h
Busulfan	Cancer	0.8 mg/kg every 6 h	≤ 12 Kg: 1.1 mg/kg every 6 h > 12 Kg: 0.8 mg/kg every 6 h
Tobramycin	Bacterial infection	3 mg/kg/day	Children: 6 to 7.5 mg/kg/day < 2 weeks: 4 mg/kg/day With cystic fibrosis: 10 mg/kg/day
Enfuvirtide	HIV	180 mg/day	11-15.5 kg: 54 mg/day 15.6-20 kg: 72 mg/day 20.1-24.5 kg: 90 mg/day 24.6-29 kg: 108 mg/day 29.1-33.5 kg: 126 mg/day 33.6-38 kg: 144 mg/day 38.1-42.5 kg: 162 mg/day
Oseltamivir	Influenza	150 mg/day	< 15 kg: 60 mg/day 15-23 kg: 90 mg/day 23-40 kg: 120 mg/day
Nelfinavir	HIV	2.5 g/day	7.5-8.5 kg: 0.8 g/day 8.5-10.5 kg: 1 g/day 10.5-12 kg: 1.2 g/day 12-14 kg: 1.4 g/day 14-16 kg: 1.6 g/day 16-18 kg: 1.8 g/day 18-22 kg: 2.1 g/day
Digoxin	Heart failure	1.4-4.0 µg/kg/day	Children: 3-8 µg/kg/day Infants: 7.5-12 µg/kg/day Neonates: 4-8 µg/kg/day

Figure 1.

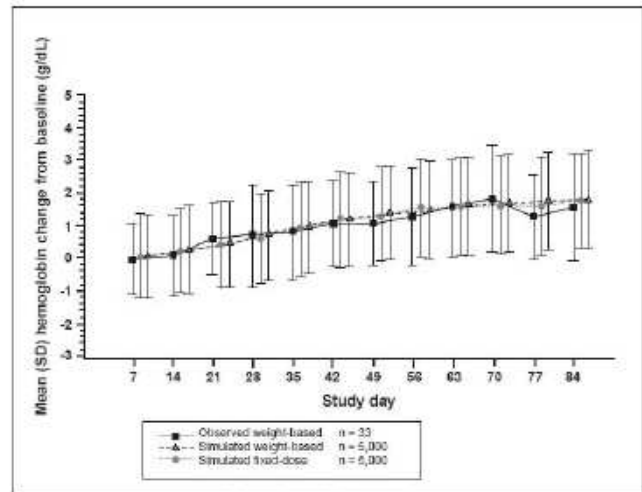
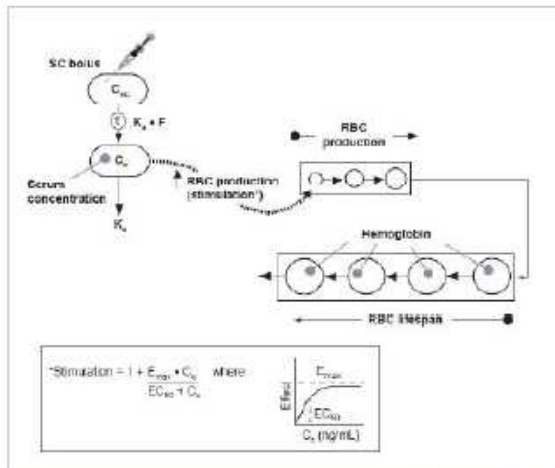


Figure 2.

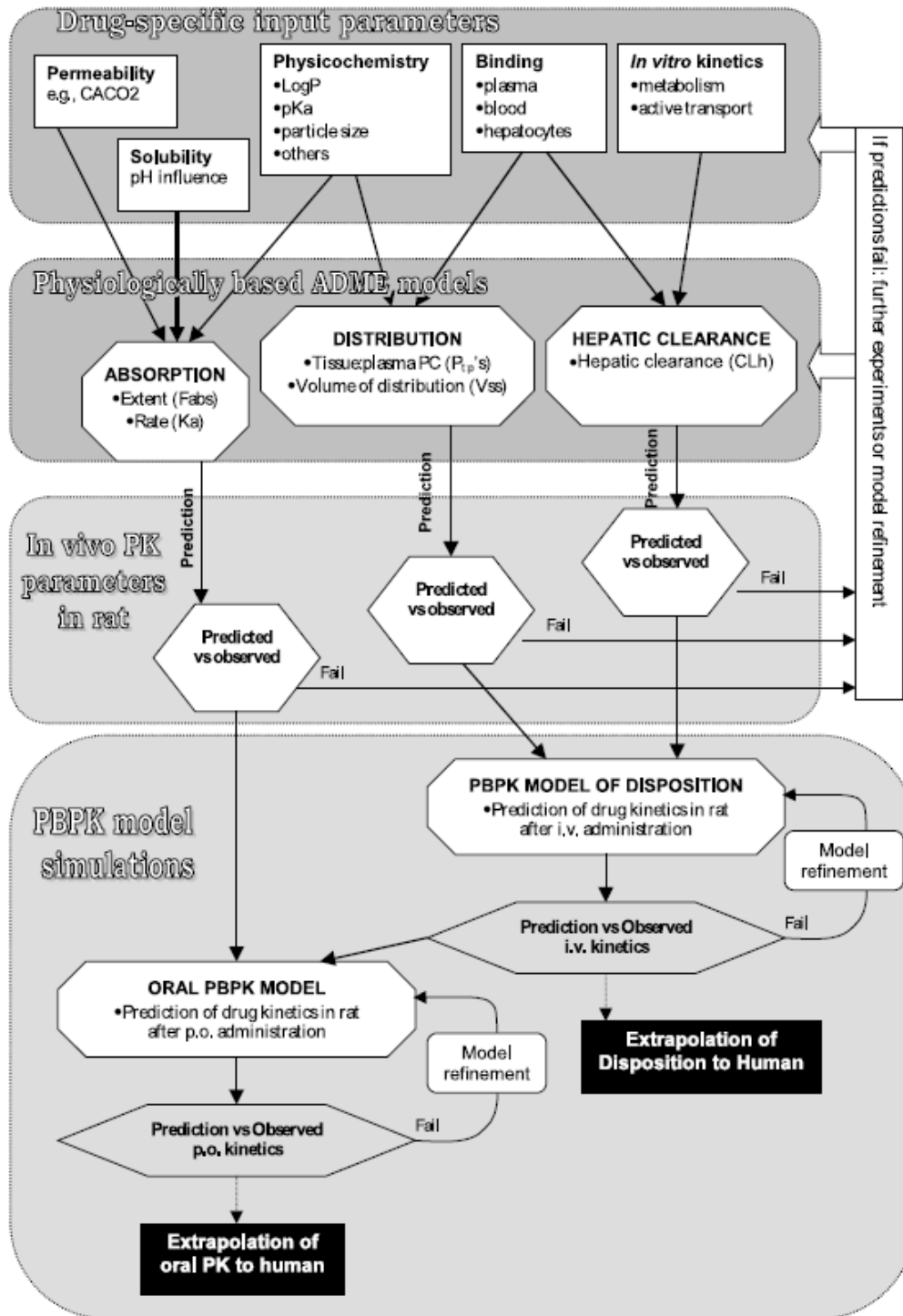


Figure 3.

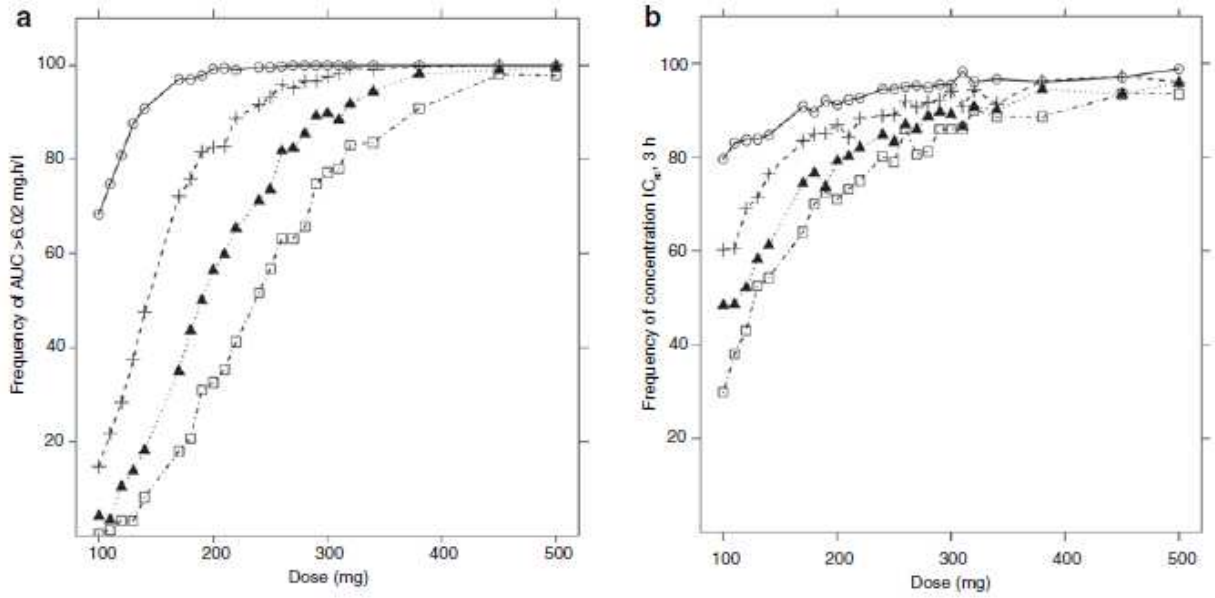


Figure 4.



Figure 5

