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Role of Modelling and Simulation in Paediatric Investigation Plans

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Abstract

Ethical and practical constraints encourage the optimal use of resources in paediatric drug development. Modelling and simulation has emerged as a promising methodology acknowledged by industry, academia and regulators. We previously proposed a paradigm in paediatric drug development whereby modelling and simulation is used as a decision tool, for study optimisation and/or as a data analysis tool. Three and a half years since the Paediatric Regulation came into force in 2007, the European Medicines Agency has gained substantial experience in the use of modelling and simulation in paediatric drug development. In this review we present examples on how the proposed paradigm applies in real case scenarios of planned pharmaceutical developments. We also report the results of a paediatric database search to further "validate" the paradigm. There were 47 out of 210 positive Paediatric Investigation Plan (PIP) opinions that made reference to modelling and simulation (data included all positive opinions issued up to January 2010). This reflects a major shift in regulatory thinking. The ratio of PIPs with modelling and simulation rose to two in five based on the summary reports. Population pharmacokinetic (POP-PK) and pharmacodynamics (POP-PD) and physiological based pharmacokinetic models (PBPK) are widely used by industry and endorsed or even imposed by regulators as a way to circumvent some difficulties in developing medicinal products in children. The knowledge of the effects of age and size on PK is improving and models are widely employed to make optimal use of this knowledge but less is known about the effects of size and maturation on pharmacodynamics (PD), disease progression and safety.

Extrapolation of efficacy from different age groups is often used in paediatric medicinal development as another means to alleviate the burden of clinical trials in children and this can be aided by modelling and simulation to supplement clinical data. The regulatory assessment is finally judged on clinical grounds such as feasibility, ethical issues, prioritisation of studies, and unmet medical need. The regulators are eager to expand the use of modelling and simulation to elucidate safety issues, to evaluate the effects of disease (eg. renal or hepatic dysfunction) and to qualify mechanistic models that could help shift the current medicinal development paradigm.

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Introduction:

The objective of the Paediatric Regulation ([1]) (EC 1901 / 2006) is to improve the health of children in Europe by facilitating the development and availability of medicines for children from birth to less than 18 years, ensuring that medicines for use in children are of high quality, ethically researched and authorised appropriately, and improving the availability of information on the use of medicines for children. It is expected that these objectives can be met without subjecting children to unnecessary trials or delaying the authorisation of medicinal products for use in adults.

In order to meet the objectives of the Paediatric Regulation there is a need for techniques that make optimal use of the limited opportunities for clinical research with a limited number of children. Methodologies such as adaptive designs, Bayesian statistics, meta-analytic approaches, development of biomarkers and modelling and simulation are recognised by drug developers and regulators as promising techniques for increasing the quality of data and analyses in small populations ([2 3 4 5 6 7 8 9 10 11]).

In this paper we focus on modelling and simulation which is gaining momentum in paediatric medicinal development ([12]). Modelling is the science of using mathematical language to describe and quantify a system. Simulation refers to the use of these models to make quantitative predictions. Modelling and simulation methodology is based on the concept of data collection (in vitro, literature, preclinical, clinical), assumption testing (attempt to elucidate the data on the basis of mathematical/statistical models), learning (retaining assumptions that are informative of the test system), prediction (simulating outcomes on the underlying assumptions that can be used to predict and optimise future experimental outcome) and confirmation of model assumptions (when compared with external data).

The properties that make models particularly useful in drug development are summarised in Table 1. The main benefit of modelling and simulation for paediatric medicines is that it enables the use of all the available information to make decisions and optimise the conduct and analysis of clinical trials in children because there are limited opportunities to collect data in children due to ethical and practical constraints. There is a risk that existing information is not applicable to a new population, but this can be identified and addressed early in development by appropriate methodological steps ([13 14 15]). A prerequisite for any analysis is data from properly conducted and well designed, recorded and reported clinical trials as described in Good Clinical Practice (GCP) Guidance([16]).

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We previously described scenarios for the use of modelling and simulation in paediatric medicines development ([17]). Modelling and simulation was identified as a tool to navigate in the paediatric decision tree and as a study optimisation and data analysis tool. The objective of this work is to "validate" the proposed paradigm through a retrospectively analysis of all positive opinions and corresponding summary reports for Paediatric Investigation Plans (PIPs) from 2007 to 2010. The terms used in the data mining and analysis exercise are defined in Table 2 and in Figures 1 & 2.

Role of Models in Paediatric Investigation Plans

Models can facilitate decision making and navigation through the different paediatric scenarios (decision tool, Figure 2) by parameterising and visualizing data. Disease models can help disentangle the different parameters that affect disease progression and responses to interventions, and can facilitate the decision on extrapolation. PK/PD models can help better compare the concentration response relationship between different age groups. Finally, models can link PD measures with clinical outcome. The PD parameter may then be used as a surrogate means to assess efficacy in different age groups.

Information available from adults and children can be used along with appropriate scaling factors to simulate paediatric data. Different study designs can be evaluated and optimised, and the optimal dose can be defined based on prior information in adults or children (study optimisation tool). When paediatric data are available, models can be used to infer results from limited sample sizes which minimises the experimental burden in children (data analysis tool). This enshrines important principles of research ethics in that as few children as possible should be exposed to risk (for example of a new drug), and invasive procedures such as blood sampling. Blood sampling should be performed in the least distressing way and using the fewest possible number of samples. This is particularly important in children who hate needles!

The basic element of a paediatric development plan is whether or not extrapolation of efficacy is possible from adults or paediatric groups; safety cannot be extrapolated. The key questions for the extrapolation is the similarity of the disease, the similarity of response and the availability of PD measurements considered surrogates for efficacy. Models are useful tools but in principle the main weight of evidence on which extrapolation is based comes from clinical data. Also the regulatory criteria for accepting extrapolation

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and/or modelling as pivotal evidence may take into account factors other than the ones mentioned in the decision tree (e.g. like feasibility of trials, ethical constraints and unmet medical need). A rule of thumb would be to follow the decision tree and propose the use of modelling and simulation when designing the development plan in children, but in the context of the specific product and clinical condition.

Examples of modelling and simulation use in Paediatric Investigation Plans

Example 1: Extrapolation from older to younger patients

At one end of the spectrum, the PIP case of an antiretroviral (HIV) drug (Drug Z) is presented. For HIV drugs PK and PD activity (viral load, CD4+ counts) are well recognised parameters for extrapolating efficacy data from adults to children ([18]). Factors that favour the extrapolation are the understanding of the target (HIV virus), the pharmacological effect and the disease "similarity" across different ages. In this context, modelling and simulation plays an important role in optimising the safety-PK/PD studies to support extrapolation and the analyses of the data generated in the studies.

Drug Z

Target Indication:

- Treatment of HIV-1 infection in antiretroviral treatment-experienced adolescents and children.

Data available at the time of PIP submission:

- Adult treatment efficacy and safety data.
- PK data in children (older age group 6-17 yrs).

Challenges:

- Paediatric dose?
- What kind of data for an indication in children?
- How to make optimal use of the previous knowledge with the product?

Sponsor's proposal:

The sponsor proposes single arm trials to evaluate the safety, tolerability and antiviral activity of drug Z using a staggered approach from older to younger children. PK and safety data from older groups will be available before progression to younger age groups. Efficacy seen in adults will be extrapolated to children on the basis of PK, PD (viral load, CD4+counts) and safety. For dose calculation the sponsor is

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targeting the same PK exposure showing activity in adults. Taking into account the differences in PK between adults and children and between different paediatric age groups the dose is adjusted to the paediatric population. Initially, the paediatric dose in the older age group (6-17 y) was defined by allometric scaling ([19]) based on the adult dose. Following the availability of PK data in the 6-17 age group modelling and simulation is to be used to describe exposure as a function of age and weight and to propose dose recommendations for the subsequent 2-6 years, 1-2 years and 2 months-1 year age groups. The PK model will be updated as PK data from each group becomes available. The population PK model will be also used for power calculation and sampling optimisation of the PK trials in children. The optimisation of studies will be based on precision and bias of mean clearance. The model assumptions and dose recommendations will be verified by PK/PD data in children. Population PK/PD models will be used to analyse PK & PD data across different age subgroups.

PIP discussions:

The role of modelling and simulation was acknowledged by the Paediatric Committee and the extrapolation was agreed on the basis of PK, viral load and CD4+ counts.

Lessons learnt:

Modelling and simulation was agreed in the PIP opinion as a study optimisation and analysis tool. The sponsor guaranteed that model assumptions and doses would be confirmed by external paediatric data; this analytical process raised the weight of modelling and simulation in the regulatory assessment. In cases where similar disease progression and response to intervention is expected between adults and paediatric groups and there are good biomarkers for activity, PK-PD is a well-accepted surrogate for efficacy (Scenario 2).

Example 2: Extrapolation from another drug with similar mechanism of action authorised in adults and children, and from adult data with the new drug.

At the other end of the spectrum are drugs for the treatment of epilepsy([20]), which constitute a vast ensemble of diverse clinical sub entities that differ by age of onset, type of seizure, aetiological background, resulting handicap, prognosis and response to treatment. We present how adult data from new

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drug N can be used to optimise the design of clinical paediatric trials for drug N supported by information on a similar product A authorised in both adults and children.

New Drug (N)

Target Indication:

- Partial-onset seizures (adjunctive treatment).

Data available at the time of PIP submission:

- New Drug (N)
  - Adult Phase II data in partial-onset seizures (adjunctive treatment).
- Existing Approved Drug (A)
  - Adult efficacy and safety data in partial-onset seizures partial-onset seizures (adjunctive treatment).
  - Children efficacy and safety data in partial-onset seizures (adjunctive treatment).
  - Same mechanism of action between A and N.
  - Different Potency between A and N.

Challenges:

- Paediatric dose?
- What kind of data are required for partial-onset seizure indication in children (adjunctive treatment)?
- How to make optimal use of the previous knowledge with the new drug N in adults and similar product A?

Sponsor's proposal:

Dose-ranging studies and placebo-controlled safety and efficacy trials in children with refractory partial-onset seizures are planned to support the indication. Interrelation and the extrapolation of the disposition properties and of the exposure-response relationship between adults and children are investigated using a sophisticated modelling and simulation approach. A dose-response (reduction in seizure frequency) model is used to predict the effective dose range in children using seizure data with drug A in adults and children,

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and seizure data of new drug N in adults with partial-onset seizures. This model is validated by concordance of predicted and observed effective doses of drug A in children. A PBPK model is used to predict the PK of the new drug N in children. This model is validated by concordance of observations and predictions for drug A in adults and children and for new drug N in adults. A population PK model is used to analyse the PK data for drug N in children when available and confirm the PBPK model predictions. Clinical trials simulation will further optimise the design of the planned paediatric studies.

PIP discussions:

The critical role of modelling and simulation is particularly noted and appreciated. For partial-onset seizures (adjunctive treatment) extrapolation of efficacy from adults could be possible. However further investigations are required in paediatric epilepsy syndromes where extrapolation is not possible (Scenario 4).

Lessons learned:

State of the art modelling and simulation was proposed by the sponsor. Modelling and simulation was agreed in the PIP opinion as a study optimisation and analysis tool. All assumptions will be confirmed by observed external data providing extra assurance on the use of modelling and simulation. Of key importance is that modelling and simulation is a learning process that can be applied across different product developments.

Paediatric Investigation Plan database search to validate the drug development paradigm

In an effort to further "validate" the paradigm proposed, all positive PIP opinions, from July 2007 - January 2010 were manually screened for any reference to modelling and simulation. The non-confidential parts of the opinions are publicly accessible in the European Medicines Agency website([21]). Also the summary reports corresponding to positive opinions were checked for consistency and completeness of the information. The data were analysed based on the terms specified in Table 2 and Figures 1 & 2.

There were 47 out of 210 positive opinions that made explicit reference to modelling and simulation, which means that sponsors are also bound to the elements of the opinion with respect to M&S. Additional search in the summary reports (non-binding) of the positive opinions identified that opinions report approximately half of the M&S approaches used in PIPs. We classified the 47 opinions that made explicit

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reference to modelling and simulation by model type used according to the definitions in Table 2. Figure 3 represents the positive opinions by model type. Population PK models represented the majority of the models referenced in the positive opinions while exposure/Dose-Response models were rare. Modelling and simulation was mainly used for dose prediction, study optimisation and data analysis rather than for navigation through the paediatric decision tree.

Discussion

There is an increasing role of modelling and simulation in drug development and a commitment from regulators to adopt this technique to alleviate the burden of clinical experimentation in children. Whether the difference between opinions and summary reports is related to the relative weight of modelling and simulation in the PIP (only the minimum binding requirements are included in the opinion) or to other factors needs to be further clarified. Nevertheless, reference to modelling and simulation in the opinions constitutes a major evolution in regulatory thinking in that the PDCO binds the sponsor to conduct and report modelling and simulation to fulfil specific objectives. To further standardise the reporting and evaluation of modelling and simulation in PIPs, a structured and explicit presentation of models and simulations in PIP submissions is recommended.

Medicine developers and regulators are more familiar with the use of population PK and PBPK models; important research has been performed and is ongoing on the characterisation of the parameters that account for differences in PK between age groups. Further consolidation of the approach is however needed from both sponsors and regulators. The effect of age on PD targets is less understood and there is a lack of mechanistic models and biomarkers for PD responses. Disease models could not be identified in our dataset. This was not unexpected because these models are in their infancy for children. We anticipate that as the knowledge in the paediatric field accumulates, disease models will become more abundant in the literature and used in the PIPs more frequently. Safety models were also not identified. The lack of safety models in the pre-authorisation phase is mainly due to the fact that it is difficult to predict drug safety based on the pharmacological and toxicological properties of the medicinal products. The safety models available in the literature consist of statistical non-mechanistic models based on large post-marketing datasets. Further advancement of disease and safety models will probably stem from progress in

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the field of systems biology[22]. Current research in areas such as genomics, transcriptomics, metabolomics, proteomics, using high throughput techniques, generate enormous quantities of new data that can be used to develop and validate models and biomarkers. Links between such data and models with medicinal development and clinical practice is challenging, although some of these methods have already found applications: e.g. investigation of the effect of genetic polymorphism of cytochromes on the efficacy and safety of medicinal products[23], determination of genetic variants that inform on the positive or negative disease prognosis and treatment outcome. Ultimately these platforms could shift the focus of medicinal development from disease - age specific endpoints to biological system specific safety and efficacy biomarkers that could be qualified along with mathematical functions as surrogates for clinical efficacy and safety. Even if this area is in its infancy, the European Medicines Agency has created a forum for such discussions with the qualification of novel methodologies procedure ([24]).

The use of modelling and simulation as a tool to navigate through the different paediatric decision tree scenarios was not identified in the search performed. The authors believe that the lack of disease and mechanistic response models is one explanation. These models are needed to provide the quantitative platform to answer the key question on the similarity of disease and disease progression between different age groups (Figure 1: Question 1 & 2). Models are used to compare concentration response between age groups in order to inform dose finding but not to define an extrapolation strategy (Figure 1: Question 3). This is probably due to the fact that when designing the PIP there are not enough PK/PD data from the product in the paediatric population to enable model building for robust and sensitive PK/PD comparisons. The lack of PD and efficacy data in paediatric populations is also the reason for not identifying models used to quantify the relationship between PD biomarkers and efficacy in order to decide on the need to conduct PK/PD or efficacy trials (Decision tool: Question 4). This is because navigation through the decision tree is based on clinical practice and quantification of the differences between age groups is of secondary importance. By implementing models in drug development and accumulating knowledge in databases and models this paradigm might also be shifted from experience based to a more integrative and quantitative approach of all data sources available.

The paradigm proposed in our previous publication is applicable to real case PIPs. Modelling and simulation is gaining weight in PIPs and is well recognised by industry and regulators as a study

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optimisation and data analysis tool. Modelling and simulation facilitates the extrapolation of efficacy between different age groups but the critical data (PK, PD, safety and efficacy) generally come from well conducted clinical studies following largely the principles described in the paediatric decision tree. The weight of modelling and simulation in the regulatory assessment is ultimately judged on clinical grounds (e.g. feasibility, ethical issues, prioritisation of studies, unmet medical need); but there has been a major shift in regulatory thinking where modelling and simulation had traditionally been seen as exploratory analysis, performed under the responsibility of the sponsor. The regulators are eager to expand use of modelling and simulation to elucidate safety issues, to evaluate the effects of disease (eg. renal or hepatic dysfunction) and to qualify mechanistic models that could help shift the current medicinal development paradigm.

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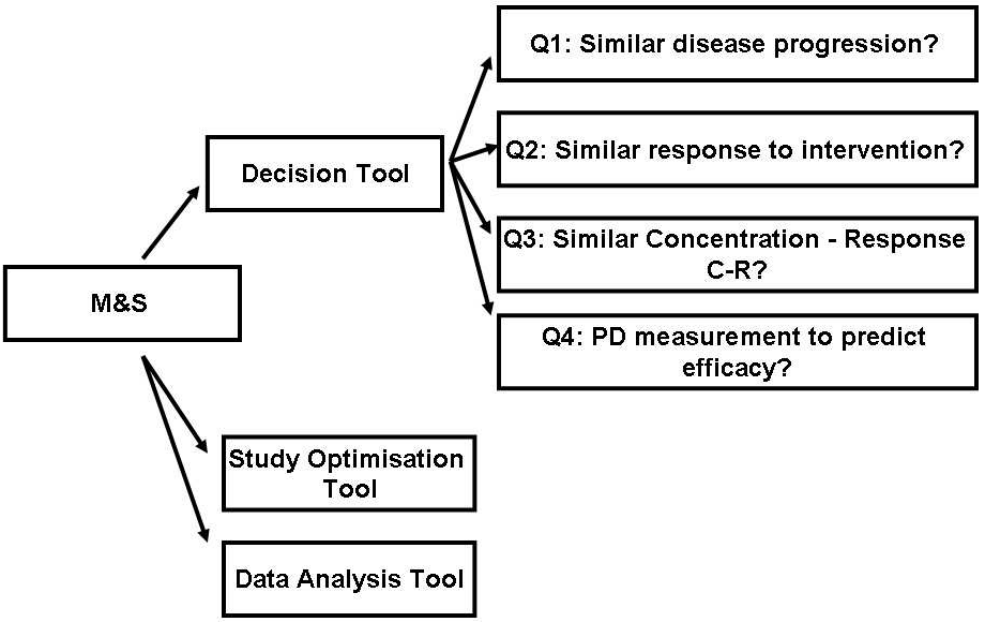

Figure 1: M&S role in PIPs.
247x174mm (96 x 96 DPI)

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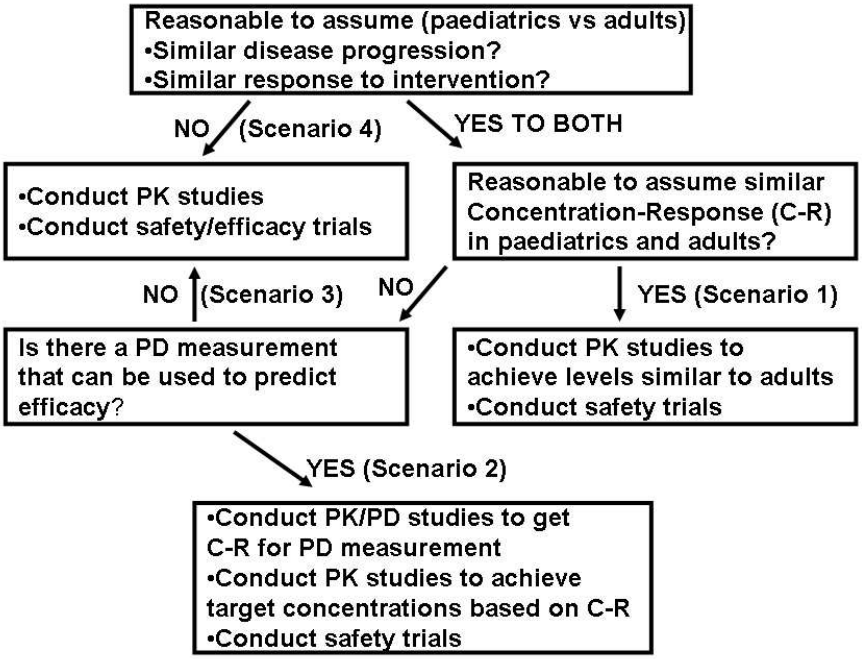

Figure 2: Paediatric study decision tree with identified scenarios.
254x180mm (96 x 96 DPI)

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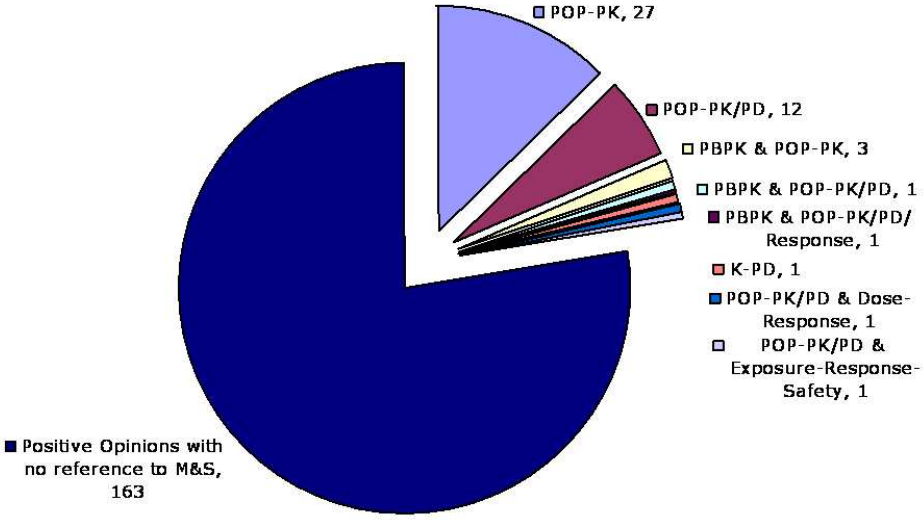

Figure 3: M&S in positive PIP opinions (as of Jan 2010). Model types and the number of opinions with reference to the specific model types.
254x158mm (96 x 96 DPI)

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Table 1: Properties that make models particularly useful in drug development
Possibility to *compile data* from different sources (in vitro, in vivo, literature, in house, different population, different medicinal product with similar mechanism of action). *Parameterisation of data*, in a way that it can be easily understood and reported. A dataset includes intrinsically all the information but cannot be used as such in order to enhance the understanding of a drug and make decisions. Usually some king of statistical analysis is required. Models can explain the different sources of variability and describe the data mechanistically. *Graphical display of data*, which makes decision making easier and information visible also to non pharmacometricians. Possibility to *simulate clinical trials* based on different scenarios (set of assumptions). The simulations can help decision making and optimise future trials. Models can be used to *drive inference* minimising the number of individuals and samples needed in clinical trials. For example sparse sampling using population PK models is well established in paediatric trials and alleviates the burden of full sampling in children. It should be highlighted that although the use of M&S for data analysis is not controversial in the case of exploratory analyses, it is disputable from a regulatory perspective when used for pivotal efficacy claims.

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Table 2: Definitions
Terms used in the document related to the paediatric regulation: *PDCO:* The Paediatric Committee (PDCO), a multidisciplinary scientific expert committee, was established at the European Medicines Agency in 2007. It is primarily responsible for the assessment and agreement of PIPs and waivers. *PIP:* The Paediatric investigation plan, including information on the quality, preclinical and clinical development, as proposed by the sponsor. The plan is discussed modified and agreed or refused by the PDCO. *Summary report ([18]):* The report generated by the European Medicines Agency on the evaluation of the PIP application. The report includes comments on the PIP and a scientific discussion on the different issues. The summary report is not binding to the sponsor. *Positive opinion:* An opinion from the paediatric committee that agrees on a PIP. The opinion on a PIP includes the minimum requirements (key binding elements) to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population. The opinion is binding to the sponsor.
Models definition based on Manolis and Pons (2009): *PBPK models* are mechanistic models mathematically transcribing anatomical, physiological, physical, and chemical descriptions of the phenomena involved in the complex absorption, distribution, metabolism and excretion (ADME) processes. *PBPK-PD:* PBPK models incorporating also a pharmacodynamic component. *POP-PK:* Data-driven compartmental models that describe the dose–concentration relationship by combining structural, statistical and random components to address different sources of variability. *POP- PK/PD:* POP-PK models including also a link between exposure and PD effects. *Disease models:* (Mechanistic) models describing the natural course of the disease. *Response models*: Response to intervention defined as a change in clinical endpoints vs. dose or PK exposure. *Kinetic (K)–PD models*: PD models developed for the description of drug action kinetics in the absence of drug concentration measurements. *Toxicity/adverse events models (safety models):* Describe the safety of the medicinal product as a function of the PK exposure or dose.
Other terms: *Biomarkers:* Measurable characteristics that are indicators of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions (adapted from ICH Topic E15([19])). *Surrogate endpoint:* Biomarker intended to substitute for a clinical endpoint. *Extrapolation* is the use of data (in vitro, in silico, PK, PD, safety, efficacy) acquired in one population and/or experimental setting to make inference about another population of interest.

Table 3: Paediatric decision tree scenarios
Each scenario requires a thorough understanding of the pathophysiology of the disease, the developmental differences between adults and children that could have an impact on PK, PD safety and efficacy and of the mechanism of action of the drug. Any doubt will make extrapolation of the efficacy questionable. *Scenario 1:* Extrapolation of efficacy is possible between adults and children based on achieving similar PK between the two populations. In practice we assume similar therapeutic effect with the same PK exposure. *Scenario 2:* Extrapolation of efficacy is possible between adults and children based on achieving similar PD between the two populations. In practice we assume similar therapeutic effect with the same PD value. *Scenario 3:* Extrapolation of efficacy is not possible between adults and children even if disease progression and response to intervention can be considered similar. The reason for this is that there is not a PK or PD measurement that can be used as a surrogate for efficacy. *Scenario 4:* Extrapolation of efficacy is not possible because the disease and response is not considered similar between adults and children. The scenarios are described for extrapolation between adults and children but can be also applicable for extrapolation between different paediatric age groups.

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