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3 Reflection paper on extrapolation of efficacy and safety in 4 paediatric medicine development

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Reflection paper on extrapolation of efficacy and safety in paediatric medicine development

Draft

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1. Executive summary

This reflection paper proposes a framework for extrapolation of data from adults to children which could serve as a basis for regulatory decision making for Paediatric Investigation Plans. Extrapolation for paediatric medicines development is discussed as a model situation but the underlying principles may be extended to other areas of medicine development.

It is acknowledged that development of a medicine in adults provides a rich source of data to inform paediatric development and given reasonable similarity between adults and children, extrapolation from adults (source population) may reduce paediatric data requirements to make conclusions for use of the medicine in children (target population). This reduction in requirements is of benefit, for ethical reasons as it may minimize exposure of children to studies and because the available paediatric population for study may be limited in number. Therefore, the use of information from adults and other sources should be maximized. Additionally extrapolation principles may be applied for rational interpretation of the limited evidence in the target population in the context of data from other sources.

The proposed framework provides the basis for an explicit and systematic approach to extrapolation to support paediatric medicine authorisation. The totality of data should allow to:

- conclude on appropriate doses in the various age groups; and
- conclude on efficacy and safety and the benefit-risk balance in the target population.

The principal elements of the extrapolation framework are:

- **Extrapolation concept**: To build on a systematic synthesis of all available data, including the use of modelling and simulation approaches, with the aim of developing explicit predictions regarding differences of pharmacokinetics/pharmacodynamics (PK/PD), disease progression, and clinical response to treatment between source and target populations.
- **Extrapolation plan**: To propose optimal studies in the target population in accordance with the degree of predicted similarities and certainty of predictions as identified by the extrapolation concept.
- **Confirmation & extrapolation**: To confirm the extrapolation concept by relevant emerging data as it is obtained in studies and to interpret the data in the target population in the context of information extrapolated from the source population(s). If the extrapolation concept cannot be confirmed in its entirety, it should be updated and the extrapolation plan revised accordingly.
- **Mitigating uncertainty and risk**: The limited data generated in the target population may not be sufficient to resolve all uncertainties and assumptions underlying the extrapolation concept by the time of marketing authorisation. Additional follow-up data, may be necessary to address uncertainties and to further evaluate assumptions. Measures to generate these data need to be proposed.

In summary, by systematic synthesis of evidence from the source population(s) and explicit quantification of the impact of differences between populations (i.e. clear identification of the gaps in knowledge) and by optimally planned studies, the data generated in the target population can be maximally informative for regulatory decision making.

2. Introduction

The Paediatric Regulation came into force in the European Union (EU) on 26 January 2007. The Regulation aims to ensure that medicines for use in children are of high quality, are ethically researched and are authorised appropriately. It aims to achieve this without subjecting children to unnecessary trials.

The number of children that can be subjected to studying a particular medicine is frequently restricted, due to the rarity of many paediatric diseases, heterogeneity of children with respect to age, development, and co-morbidity, and issues around consent to study participation. For these reasons, it is often not possible to generate a full data set in the paediatric population according to the usual regulatory standards. However, development of a medicine in adults will present a rich source of data and understanding that can inform the design of a paediatric programme which may potentially allow a reduction in paediatric data requirements for conclusions in paediatric populations, without reducing evidentiary standards. Consequently, it is important to bring all relevant evidence available from various sources to bear on regulatory decision making for children.

As outlined by the principles discussed in the 'ICH E11 Clinical Investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99)' and 'Role of Pharmacokinetics in the development of medicinal products in the Paediatric Population (CHMP/EWP/147013/2004)' given reasonable similarities between adult and paediatric patients and between paediatric patients of different ages, extrapolation may be used.

The following working definition for extrapolation has previously been proposed by the EMA Concept paper on extrapolation of efficacy and safety in medicine development: 'Extending information and conclusions available from studies in one or more subgroups of the patient population (source population(s)), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product.

The decision to extrapolate will require the timely availability of useful source data but will ultimately depend on a value judgment on the trade-off between the uncertainties of extrapolation and the additional patient resource required to carry out further studies. Extrapolation can only be justified when it is the result of a careful and explicit scientific process that eventually gives rise to knowledge gain, rather than an intuitive leap of faith that may undermine the possibility of further scientific knowledge generation.

However, accepting and implementing extrapolation for medicine development is challenging for many reasons. It is difficult to predict age-related differences in PK, PD efficacy and safety. Therefore, there is the need to develop a systematic inventory and qualification of the paediatric specific tools for extrapolation (in vitro models, animal models, biomarkers, endpoints, experimental designs, analytical assays, data analysis tools, systems pharmacology approaches, better in-silico tools); to define criteria to assess the quality of available data; standardise methods and decision criteria for extrapolation; and strategies that help to manage uncertainty and risk associated with reduced data requirements.

This reflection paper has been developed by EMA committees, methodology working groups, and external stakeholders. The expertise within the EMA Extrapolation group includes clinicians, pharmacologists, pharmacometricians and statisticians from the EMA and National Competent Authorities and from Academia.

3. Scope

The objective of this reflection paper is to propose a framework that supports an explicit and systematic approach to extrapolation which sets out i) when, ii) to what extent, and iii) how extrapolation can be applied and validated.

To this end, within this paper, the original framework proposed in the Concept Paper has been refined with methodological approaches and decision criteria for extrapolation proposed. Current knowledge has been summarized and areas that need to be further developed also identified.

Specific extensions of the existing algorithms for extrapolation in paediatric medicines development are proposed such as:

i) Systematic assessment and synthesis of existing data, including the use of Modelling and Simulation (M&S) on the similarity between source and target population on several levels (PK/PD, disease progression, clinical response);

ii) Quantitative (rather than qualitative) predictions on the degree of similarity in the target population;

iii) Development of a framework for reduction of the required evidence generated in the target population in accordance with the predicted degree of similarity;

iv) Iterative loops of prediction, data generation and confirmation, or adaption of the development plan, using M&S in the planning and analysis of paediatric studies;

v) Continuing confirmation/adaptation based on iterative loop.

It is anticipated that the data generated to confirm the extrapolation concept within the development of a medicine can be, if applicable, of use for PIPs and to avoid unnecessary studies; therefore while increasing experience with extrapolation approaches over several development programmes for specific therapeutic areas or medicines, the requirements for individual developments may evolve.

It is acknowledged that the application of extrapolation varies by population, therapeutic area, and medicinal product and it is not possible to develop at this stage a general algorithm for extrapolation. However the framework is addressing a set of methods and approaches that can be used for an extrapolation exercise with a view to avoid unnecessary studies and where the efficiency of the design or analysis may be increased. The general principles presented are by no means exhaustive but should encourage further exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify the choice of strategy.

Additionally extrapolation principles may be applied for rational interpretation of the limited evidence in the target population in the context of data from other sources.

The Agency encourages applicants and Marketing Authorisation Holders to primarily follow the relevant therapeutic area CHMP guidelines. From the existing CHMP Guidelines there may be products or areas for which it is currently foreseen that extrapolation will not be possible and deviations from this should be prospectively considered and be fully justified. This Reflection Paper provides a framework for how such a justification should be structured and the Agency advises applicants to discuss any proposed deviations with EU regulators during medicine development with the Paediatric Committee (PDCO) and through Scientific Advice.

Where a therapeutic area guideline clearly defines the rationale for extrapolation in the paediatric population, and lays out the totality of the data expected from an extrapolation approach, these should be followed unless justified. In other cases where the possibility of extrapolation is discussed, but a

case-by-case basis is foreseen, or no clear guidance as the expected data requirements is provided, this Reflection Paper provides the framework for the exercise.

Notwithstanding a key focus of the framework is on areas where extrapolation is not yet considered as a regulatory standard in therapeutic guidelines, in order to set out a structured approach to be followed. Additionally the framework may be used when extrapolation of efficacy is acceptable and it is applied to optimise the dosing rationale strategies.

This document is intended to assist applicants during the development of medicinal products for paediatric patients, to improve interactions between stakeholders including a better utilisation of patient involvement in clinical research and to standardise decision making on extrapolation approaches.

This reflection paper should be read in conjunction with the introduction and general principles of the Annex I to Directive 2001/83/EC as amended, as well as European and ICH guidelines for conducting clinical trials.

4. Proposed Framework:

A. Rationales for extrapolation:

i) To avoid unnecessary studies:

The primary rationale for extrapolation is to avoid conducting studies in children if the prevailing data and scientific understanding is such that the scientific questions of interest can be properly addressed through available evidence. For ethical reasons, the goal is to minimise the number of children subjected to studies and trial burden and to maximise the information extracted from other sources without compromising the evidence base for any regulatory decision.

In addition, extrapolation may serve to allocate resources to those areas where studies are most needed. For example, fewer data may be needed in adolescents if they are reasonably similar to adults (but some data are usually needed for bridging). Rather, paediatric development should focus on those age subsets or disease subsets where least extrapolation is possible due to the largest differences to adults, typically infants and neonates.

ii) Optimising decision making when patients are scarce:

As per the principles outlined in the guideline on clinical trials in small population in situations where there are only a few patients available (orphan disease, paediatric age subsets, etc.),no methods exist that are relevant to small studies that are not also applicable to large studies, however less conventional and/or less commonly seen methodological approaches may be acceptable if they help to improve the interpretability of the study results. In small populations, it is even more important to ensure that all the available scientific knowledge is summarised in advance, and that the study(ies) conducted truly answer the most important scientific questions as best they can.

In this situation the extrapolation principles and tools may be applied for a rational interpretation of the limited evidence in the target population in the context of data from other sources. By systematic synthesis of evidence from the source population(s) and explicit quantification of the differences between populations, the robustness of data generated in the target population can be better quantified, and conclusions drawn for the target population.

Ethical reasons for extrapolation and challenges related to situations with limited number of patients are frequently intertwined and may even be conflicting. For example, neonates and infants tend to have the greater developmental differences compared with adults, which may limit extrapolation where

no older paediatric age group data are available and/or where no data from similar compounds are available, but the feasibility of studies in this group is most severely restricted.

B. Extrapolation concept:

B.1. Basic mechanisms / Qualitative data assessment

The initial step in formulating an extrapolation concept is to define the extrapolation target in terms of population(s) (e.g. paediatric age groups), medicinal product in the same class, and condition(s), and to identify all possible source data, in terms of populations (e.g. adults), medicinal products, or similar conditions.

Data sources that should be assessed include in vitro, preclinical, epidemiological studies, diagnostic studies, PK and PD studies, biomarkers/ surrogates to clinical endpoints (e.g. assessment of pain) that could be used in all paediatric age subsets as well as in adults regardless of the stage of cognitive maturation, clinical trials and observational studies with standard therapy for the indication under development, the medicine of interest or in the same class. In addition, literature data on the maturation of organ/target systems, which are relevant to the mode-of-action, PK, PD, efficacy or safety profile of the respective medicine, should be considered.

All existing data should be systematically reviewed to describe the mechanisms and characterize differences between source and target population on the following aspects (table 1):

- Medicine disposition and effects: Absorption, distribution, metabolism, excretion; mode of action, pharmacodynamic effect, exposure-response relationship; safety, sensitivity of the developing organism to certain drug-related toxicities as described for the adult population; including assessment of patient-related characteristics that may influence the above.
- Disease manifestation and progression: Relative prevalence of disease subtypes based on aetiology, pathophysiology; differences in clinical manifestation between children and adults, severity, and disease progression (identify progression indicators and age-specific differences).
- Clinical response to treatment: Differences between children and adults, applicability and validation of clinical efficacy and safety endpoints in the respective populations.

Differences should be assessed between adults and children but also between paediatric age groups and relevant age cut-offs should be identified. Once data have been generated in older paediatric age groups, these may become part of the source population for extrapolation to younger age groups.

The quality, quantity and completeness of existing data needs to be systematically assessed, for example by considering the types of study designs (levels of evidence), risk of bias scores, assessing publication bias, etc. The strength of prior evidence and how much weight can be put on is a combination of actual data and value judgements that should be synthesised in the form of an in-depth assessment with expert opinion, as appropriate. (Semi) quantitative methods that summarise these value judgements could be used here.

B.2. Quantitative evidence synthesis

Available information should be synthesised in a quantitative fashion as far as possible on the respective levels to ensure optimization of the extrapolation plan (table 1):

- PK and PD: Model all relevant available data (in-vitro, preclinical and clinical) in an appropriate model/computational platform (e.g. systems pharmacology, mechanism-based and empirical

population PK/PD approaches) to investigate or predict the relationship between dose, exposure and interaction with target (PD endpoints), and impact of potentially important covariates.

- Disease manifestation and progression: quantitative synthesis of natural course of disease data or disease models could be used to characterise differences between source and target populations in disease manifestation and progression.
- Clinical response: quantitative synthesis or meta-analysis of existing treatment data, or disease response models could be used to quantify the degree of differences between populations in clinical response (efficacy, relevant safety aspects) given similar exposure or similar PD response.

These levels should be considered in a stepwise fashion but may benefit from integrative modelling approaches that account for all these levels. Models should be refined by incorporation of new data generated on each level, as well as data generated per age group.

The differences between source and target population should to the extend possible assessed on two main axes, which are not mutually exclusive:

i) Mechanistic approach: This will be a weight of evidence approach based on quantitative and systems pharmacology modelling or simpler mechanistic models for PK/PD (e.g. PBPK) and disease. If such novel models are used, they should be qualified. It is recommended to submit mechanistic models to the Agency for qualication before submission.

ii) Empirical approach: This approach will be using available PK/PD and disease data from literature and in house experiments to build a statistical framework for extrapolation. The empirical approach requires a more comprehensive (compared to the mechanistic) statistical comparison between groups,e.g. a Bayesian framework, model based meta-analysis, and requires appropriate definitions of equivalence margins to compare between adults and children. The required strength of evidence from this comparison would be influenced by the weight of evidence coming from the bottom up approach and quantitive approaches might be useful to characterise how much evidence is required. This approach can be assessed by its operating characteristics using a wide range of assumptions.

Hypotheses on how PK scales with age could be based on PBPK models and predictions of semi-mechanistic adult population-models with appropriate scaling for body size, maturation and potential different co-variates where appropriate. Discrepancies between the two approaches should be discussed with regulators and justified with regards to the impact on the extrapolation plan.

Hypotheses on PD scaling are likely to be more complex and will need to include known or assumed system maturation properties and potentially the need for different PD outcomes, for which some sort of assumed mapping of adult PD onto the paediatric PD measure will be required.

Hypotheses on similarity of disease should as far as possible be supported by disease models, which could be empirical or mechanistic depending of the current status of knowledge in the therapeutic field. The possibility to strengthen the scientific rationale by inclusion of systems biology/pharmacology data from both source and target population should be considered when only empirical population data (epidemiological, diagnosis and non-interventional study data) are available. Approaches to quantify expert opinion could also be considered when insufficient quantitative data are available and such approaches aid the interpretation of the data.

Hypotheses on similarity of clinical response given a specific pharmacological intervention should likewise be explored by interventional disease models when knowledge allows. Whether mechanistic or semi-mechanistic models are possible will depend on the therapeutic area, but again, efforts to

strengthen the scientific rationale by inclusion of systems biology/pharmacology data from both source and target population should be considered.

In either of the above types of modelling approaches, sensitivity analysis and simulation/estimation exercises may prove useful. Sensitivity of predictions to key assumptions should be explored prior to finalising the extrapolation plan, and stochastic simulation estimation exercises performed to ensure studies are adequately powered to detect model mis-specification.

Safety information from the source population may be used to predict safety events related to the mode of action of the drug and related to dose. Appropriate dose, as extrapolated from the source population, would aim at optimizing efficacy *versus* safety in the target population. However considering that the effects related to growth and maturation cannot be extrapolated from adults, safety data will eventually be needed in the target population for confirmation and to identify unexpected (age-specific) safety events.

Additionally even if the type of adverse event is the same between adults and children, the impact between the two populations might be different.

B.3. Hypotheses/Predictions

Built on qualitative characterisation and quantitative synthesis (B1. and B.2.), the extrapolation concept should result in explicit predictions of differences in PK, PK/PD, the nature of disease (manifestation, severity, progression, etc.), and clinical response to treatment in the target population as compared to the source population (table 1). These predictions should be quantified to the greatest degree possible. In addition, expert interpretation and judgement will usually be required to weigh the existing evidence and fill in knowledge gaps. Quantitative approaches that summarise the prior information whilst integrating expert judgement could be considered as part of the extrapolation exercise, although methods to do this are still in the early stages of development.

Assessing the risk of uncertainties and assumptions at planning stage:

All sources of uncertainty should be specified, both uncertainties in the known data, for example due to the quantity and quality of data, heterogeneity of information, high variability of data, or lack of understanding, as well as the assumptions made in predicting for the target population. The uncertainty of predictions will usually increase with the degree of expected differences between source and target population. A synopsis of the uncertainties of the extrapolation concept could include what is known and not known about the medicinal product, the paediatric formulation, pharmacology, disease progression, and clinical response.

The impact of uncertainties and assumptions, i.e. the probability of violating assumptions and the clinical consequences, should be evaluated and quantified(Harnisch 2013). Various risk scenarios should be explored potentially using the models used for quantitative evidence synthesis. The confidence in predictions at planning stage is the basis for defining the requirements for generating further evidence and will influence the risk of decision making for the extrapolation plan.

C. Extrapolation plan

Built on the extrapolation concept, the extrapolation plan should clearly identify knowledge gaps (i.e. data that cannot be extrapolated from adults) and where these are of clinical relevance, any additional information or further research that might be required. This further research may not necessarily involve new studies in children but e.g. may involve new analyses of existing data or new modelling exercises. As a prerequisite, the extrapolation plan should serve to investigate the most critical predictions and assumptions for licensing purposes in the extrapolation concept.

It is envisaged that such an approach will in general lead to fewer patients being studied than would be required if a formal proof of efficacy is needed, but this may be over a higher number of smaller studies, each with different aims. The studies required may reduce placebo exposure, and ensure as many subjects as possible receive an optimal dose. In the event that the plan does not fulfil these aims, then the extrapolation approach may not be appropriate and a full development programme would be a more optimal use of resources.

Studies required for dose finding/confirmation, for characterising disease progression, and evaluating clinical response in the target population should be proposed, as summarised in Table 1 and discussed below.

The set of studies proposed in the extrapolation plan may be reduced (with regards to number and types of studies, design modifications, number of patients) in accordance with the extrapolation concept, i.e. the degree of predicted similarities between source and target population and the strength of predictions (level of uncertainties and assumptions).In general, efforts should focus on areas with the largest uncertainties, e.g. younger age subsets. For example if there is evidence of efficacy in adults, and standalone evidence of efficacy in the younger age groups, then the uncertainties in the adolescent group are substantially reduced and further efficacy studies may not be required if the dose-exposure-response relationship is consistent.

The following options should be considered:

- No extrapolation: is considered possible if there are too large differences between source and target population and large uncertainties. Thus, a full paediatric development with PK and PD studies and stand-alone evidence of efficacy and safety will be required as per default, to independently demonstrate efficacy and establish a positive benefit-risk balance. Even in these situations, modelling of prior information from source data may allow optimizing the design of paediatric studies. A full development program remains the norm against which any extrapolation proposal needs to be measured.

- Extrapolation: the extent to which extrapolation may be applied lies on a continuum involving a wide spectrum of possible reduction in data requirements with regards to the studies on various levels(PK, PD, efficacy, and safety), the types of designs, and the numbers of patients studied in the target population or subgroups of the target population. The requirements will depend on how much the source data can be used to predict for the target population in any of these aspects. The spectrum ranges from controlled efficacy and safety studies with various reductions in sample sizes (see further discussion in section C.1.2.), to non-controlled efficacy and safety studies, dose-concentration-response studies, PK or PK/PD studies only to extrapolate efficacy, or, in rare instances, no PK or PD studies in the target population. Collection of relevant safety data will always be required to identify any unexpected age-specific safety events, which may also be used to collect some descriptive efficacy data to confirm the extrapolation concept.

The initial extrapolation plan will need to be refined during intermediate development steps on the respective levels (PK, PD, and clinical response). Evidence generated should feed back into the extrapolation concept, reducing the number and degree of assumptions and allowing more precise predictions, and consequently, adapting the extrapolation plan. The extrapolation plan should encompass the whole life-cycle of paediatric development of the medicine, including post-authorisation studies, and should evolve from a predictive, assumption-based approach to a confirmatory, data-based approach.

C.1. Design of studies in the extrapolation plan

The extrapolation plan should contain all the proposed studies with a discussion of the scientific questions they are intended to answer, the uncertainties these studies should be able to resolve, and the uncertainties that will remain. If the Dose-Exposure-Response relationship cannot be clearly defined in the paediatric population, then relevant studies to generate efficacy data will need to be proposed. Key design elements for these different types of studies are discussed below.

The benefit of a staggered approach across age groups based on the safety profile of the compound as well as the need to have PK/PD information specific to each of the paediatric age groups should be balanced against the need for timely access to a medicinal product even for the youngest age groups of the paediatric population.

C.1.1. PK/PD Studies:

The dosing rationale should be informed by appropriate modelling approaches as outlined in section B.2. Modelling should be used to optimize PK/PD studies in children (design, sample size, starting doses, timing of sampling, and number of samples. PBPK models are encouraged; however with the current lack of physiological knowledge on the ontogeny of transporters and some enzymes (depending on the elimination pathway), any new information should be qualified before supporting regulatory decision. PK/safety-only extrapolations should not be proposed without very strong justification. Whenever possible, PD data should also be investigated in the target population.

Powering PK or PK/PD studies requires knowledge of the PK or and PK/PD relationships, variability and covariate effects. This is normally not the case at the specific stage of development. However models developed in other age groups or/and in other medicines with similar ADME and pharmacological targets incorporating also assumptions on growth and maturation can be used to predict the sample size and sampling times for target PK and PD parameter precision, or for other types of model based inference (e.g. covariate selection, hypothesis testing). In these cases it is recommended to account for uncertainty in the model as well as model parameters when evaluating the study design.

C.1.2. Efficacy Studies

Even when efficacy studies need to be conducted, available information may be used to optimally design these studies to provide the relevant evidence. Disease response models and clinical trial simulations could be used to optimize trial design and help inform sample sizes for pivotal clinical trials. The following design aspects should be considered carefully:

Sample size: When extrapolation is proposed to avoid unnecessary studies in children, but efficacy data is still considered to be necessary to conclude on a positive benefit-risk, then these studies should still be designed so that a clear hypothesis related to the study question of interest is stated, there is a clear idea of how success will be defined and a sample size calculated accordingly. If a reduced efficacy study is proposed then the study should be powered so that once qualitatively or quantitatively integrated with available data from the source population, the totality of evidence is adequate.

If on the other hand the aim is to provide evidence to validate the extrapolation concept, or to rule out important differences between treatment groups, then the sample size calculation may result in a different number compared to the one generated above. When an extrapolation approach is a necessity due to a limited patient population who can be enrolled in a trial, the sample size chosen will mainly be driven by the feasibility constraints this imposes.

Once it has been justified and established that an adjusted sample size is acceptable or necessary, approaches to address this include: using a larger level for the Type 1 Error than the usual 5%,

potentially based on a quantitative justification of the value chosen; widening a usually accepted non-inferiority margin, which may mean the clinical interpretation is different; using Bayesian methods to either summarise the prior information for the extrapolation concept, or to explicitly borrow information (from adult trials, from control groups, from other paediatric clinical trials). The acceptability and appropriateness of each approach will depend on the knowledge generated in the context of the extrapolation exercise, both in terms of the adult data and any paediatric data generated to date. Uncertainties in borrowing information from external data sources should be reflected in the extent to which reductions in sample size are proposed.

As data are generated through the development cycle, it is possible that the assumptions behind the parameters that have gone into the sample size calculation may need to be revisited to take into account this extra information.

If there exist subgroups identified a priori for whom it is important to generate sufficient data, stratification may be important, and recruitment may need to specify a minimum number of patients to be recruited in each subgroup (for example subsets based on pubertal development stage).

Choice of control group: Even if data requirements are reduced in the target population, comparative studies are preferable to generate estimates of response to treatment in the control arm as a frame of reference for the comparison to studies in the source population, and to provide an estimate of effect size attributable to active treatment, although confidence intervals will be wide.

The formal incorporation of historical controls is possible, but inherently introduces different uncertainties to such comparisons. Such estimates will allow comparison of baseline disease progression and treatment response between target and source population (as indicators of similarity). A prerequisite for these comparisons is that trial design and endpoints are reasonably similar between adults and children.

Randomisation: Randomisation methods should be employed that maximise the amount of robust information available from the study. This also includes safety information, and the optimal study design may involve a different randomisation ratio, for example 2:1, to ensure sufficient safety data is collected with active treatment. In addition, asymmetric randomisation reduces the number of patients exposed to placebo, where this is deemed useful.

Endpoints: Endpoints chosen should ideally be clinically relevant to the paediatric population, and should be sufficiently sensitive to enable the study to detect a clinically relevant difference between treatment groups if one exists. The latter point is especially important if the patient population is limited by feasibility constraints. In general, continuous endpoints are more sensitive than time-to event endpoints, which are in turn more sensitive than binary data. Even if commonly used to define clinical relevance, choosing a binary primary endpoint on which to formally demonstrate statistical significance, oftentimes called a responder analysis, may not be optimal for trial design. One approach to extrapolation where responder analyses are the default primary estimation method in adult studies is to first statistically determine whether or not the treatment effect is real on the original, continuous scale. The next step is to determine clinical importance by examination of response rates, possibly using various response definitions. Such an approach may mean that other approaches outlined in the section on Sample Size above, in terms of changing alpha, widening the non-inferiority margin, or the use of Bayesian methods, may not be necessary.

Where possible and relevant, it may be prudent to validate potential paediatric endpoints in the adult trials. It may also be possible to use surrogate endpoints, providing that they have been validated.

The extrapolation plan should be justified on the basis of the accumulated, integrated evidence, as discussed above. The objectives and consequent size of prospective studies should aim to complete the extrapolation exercise, including the confirmation of extrapolation assumptions.

D. Analysis phase

D.1.Validation / confirmation

As well as potentially answering questions related to efficacy in and of themselves, the data observed in the target population as part of the extrapolation plan should be used to validate the extrapolation concept, specifically to validate the modelling approaches and assumptions used for extrapolation, and to confirm the PK and PD predictions, the predicted degree of differences (or understanding) in disease progression, and in clinical response.

The consistency between the predictions in the extrapolation concept and the observed data should be confirmed, ensuring that any substantial deviation from the predictions is ruled out. In most settings, a true validation of the assumption might not be possible but methods should be used that are responsive to relevant deviations from the assumptions.

If the data do not confirm the extrapolation concept, i.e. larger observed than predicted differences between source and target population, the extrapolation concept needs to be updated accordingly and, hence, the ability to extrapolate. Consequently, the need to generate more data in the target population should be assessed and the extrapolation plan adjusted.

This may be an iterative process of predicting and confirming, or adapting, when moving through the phases of clinical development, and from one age-group to the next. Adjustments may even be made during an individual trial using an adaptive design – for example choosing the optimal dose based on PK/PD confirmation early in the trial, and dropping those doses not considered optimal, while continuing to randomise patients.

When it has already been established in a specific therapeutic area guideline that extrapolation is possible, further data to validate the extrapolation concept may not be necessary

D.2. Extrapolation

If the extrapolation concept is confirmed, the data generated can be used to make conclusions for the target population. Based on the extrapolation concept, the data generated in the target population may not be self-standing to support any conclusions. Hence, the data need to be interpreted in the context of information extrapolated from the source population(s). Models can be updated with the new data to provide more precise parameters.

E. Dealing with uncertainty and risk at validation

The higher the degree of extrapolation between source and target population, the more limited will be the data set generated in the target population and conclusions will rely on information extrapolated from the source population(s). It should be noted that if a high degree of extrapolation is possible, this will inevitably result in less data being generated that can validate the extrapolation concept. This is a different source of uncertainty that may need to be addressed, possibly through post-authorisation measures.

The impact of uncertainties and risks could be evaluated at planning but also at extrapolation stage through simulations. In addition, strategies to mitigate risks and to further evaluate assumptions need

to be developed. To increase the reliability of conclusions based on extrapolation, measures to ensure the robustness should be pre-planned and criteria could be implemented such as:

- Biological plausibility supported by in vitro, preclinical or clinical data.
- Iterative loops of model building and data generation pointing to consistency of predictions with observed data.
- Concordant responses on different endpoints.
- Prospectively planned meta-analysis.
- Joint analysis of overall development program with covariate analysis, e.g. age.
- Further validation by (cumulative) post-authorisation data.
- Validation of extrapolation approaches over several developments in related conditions, or related medicines.

With increasing experience with extrapolation approaches over several development programmes for specific therapeutic areas or medicines, the requirements for individual developments may change.

F. Extrapolation in the product development life cycle

Consideration should be given to extrapolation at the early planning stages of a development program, since, when pursued, it is expected to impact profoundly on data requirements (in terms of content and timing, both in source and target population) during the course of a product development life cycle. For all the above reasons, applicants are encouraged to discuss extrapolation early on with regulatory authorities. It is indeed anticipated that opportunity for extrapolation, with anticipated benefit of early market access, will be missed when not planned and discussed early.

Extrapolation is expected to be the subject of at least two (and likely more) regulatory interactions:

- early regulatory review of extrapolation concept and plan (at the latest at the expected time of PIP application, but often likely earlier in view of impact on overall development program)
- model validation (by applicant) resulting in (iterative) refinement/correction of model
  - regulatory review of source and target data and of the results of the model validation process. If such a process suggests that the assumption underpinning extrapolation are not correct and could call into question the extrapolation concept, this can lead to:
- refutation (by applicant) of model(s) and extrapolation concept
  - regulatory interaction/PIP modification to propose/request modification of extrapolation program or discontinuation

It is envisaged that such an approach should mean that by the time the extrapolation plan has been agreed, and paediatric development commences, there are likely to be very few changes to studies in the PIP that support the extrapolation concept.

5. Conclusion

This reflection paper proposes a framework that intends to ensure harmonised and consistent decision making along the product development life cycle regarding the use of extrapolation in paediatric

population. This should result in a more rational, consistent, and more efficient paediatric drug development, and a better targeting of paediatric needs.

6. References

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			Pharmacology Drug disposition & effect	**Disease manifestation & progression**	**Clinical response to treatment** Efficacy & safety
SOURCE POULATION Adults	**Extrapolation concept**	**Mechanisms**	Age-related differences in - ADME - mode of action - PD effects (E-R) - toxicity	Age-related differences in - aetiology - pathophysiology - manifestation - progression - indicators	Age-related - differences, - applicability, - validation of efficacy & safety endpoints
		Quantitative evidence	PB-PK/PD models Pop-PK/PD models Covariates: - age, maturation, etc - disease, comorbidity,	Quantitative synthesis of natural disease data Disease progression models Covariates: - age - disease types, severity - comorbidity	Quantitative synthesis or meta-analysis of treatment data Disease response models Covariates: - age - disease types, severity - comorbidity
			➢ existing data ➢ progressive input of emerging data		
TARGET POPULATION Children, different paediatric age groups		**Prediction**	Predict doses to achieve - similar exposure, or - similar PD effect, and - acceptable safety per age group	Describe/predict differences in natural course of disease progression by age group	Given similar drug exposure or PD response, predict degree of differences in - efficacy - safety - benefit-risk balance by age group
			➢ refine predictions using emerging data		
	Extrapolation plan		PK studies or PK/PD studies needed for confirmation of doses in target population	Epidemiological data - natural disease course - SOC treatment in target population	- Design of clinical studies - Sample size(s) required in target population to conclude on benefit-risk balance
	Validation & Extrapolation		Validate - modelling approaches - modelling assumptions - confirm predicted differences in PK and PD Establish appropriate doses in the target population	Confirm predicted differences in disease progression Conclude on disease progression in target population	Confirm predicted differences in clinical response Conclude on positive benefit-risk in target population
			➢ alternatively, adapt extrapolation concept and plan		
	Further validation		PK/PD data from - phase III trials - post MA studies	Epidemiological data Other drug developments	Post MA studies Prospective meta-analyses Pharmacoepidemiological data Other drug developments

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