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Reflection paper on the use of extrapolation in the development of medicines for paediatrics

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Executive summary

For the purpose of this Reflection Paper extrapolation is defined as '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, in order to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the amount of, or general need for, additional information (types of studies, design modifications, number of patients required) needed to reach conclusions'.

The main focus of the document is to provide a framework for extrapolation as a methodology to generate evidence for regulatory assessment in a target population. Specifically the framework addresses the use of quantitative methods to help assess the relevance of existing information in a source population to one or more target population(s) in respect of the disease, the drug pharmacology and clinical response. Based on this, predictions on the expected effects of treatment in the target population can be formulated. These predictions will be conditional on certain assumptions, and a specific extrapolation plan can be developed to address gaps in knowledge and assumptions, so that the totality of available evidence can address the scientific questions of interest for marketing authorisation in the target population. The principle elements of the framework are:

Extrapolation Concept: Existing information about the disease, the drug pharmacology and the populations should be quantified. Based on the differences between source (e.g. adults and/or children) and target populations (e.g. other paediatric population), important assumptions and uncertainties about the relation between dose, exposure, pharmacodynamic response and clinical efficacy should be identified. From this exercise it can be assessed whether clinical efficacy can be predicted, e.g. *via* drug exposure (PK), a relationship between drug exposure (PK) and pharmacodynamic (PD) response or, in the absence of a quantified Pharmacokinetic (PK)/ pharmacodynamic (PD) relationship, based on other pharmacological or clinical justification. A structured documentation, including an assessment of the impact of identified assumptions and uncertainties on the predictions should be provided.

Extrapolation Plan: In accordance with the assumptions and uncertainties as identified by the extrapolation concept, specific objectives(s) and methodological approaches should be proposed for the tests and trials that need to be conducted to draw inferences that are relevant for the target population. These tests and trials should primarily aim to generate evidence that strengthens and ultimately, based on success criteria, validates the extrapolation concept. This validation confirms whether regulatory decisions can rely on the initial, or revised, predictions for the expected effects of treatment in the target population or if more data needs to be generated.

Mitigation of uncertainty and risk: As with any regulatory decision, the data generated in the target population may not be sufficient to address all uncertainties related to efficacy and safety by the time of a marketing authorisation in the target population. In some situations it may be important to gather additional data post-authorisation to address residual uncertainties.

An exhaustive list of methodological approaches is not provided. The framework should encourage exploration of potentially suitable methods for specific situations. Different approaches may be taken and the applicant should justify their choice. While the focus is on extrapolation for the development of medicines in children, the underlying principles may be extended to other areas.

1. 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. Children should have the same opportunity as adults to use safe and effective drug products.

To obtain a marketing authorisation in a specific patient population it is necessary to establish therapeutic efficacy and a positive risk-benefit in addition to ensuring the quality of the medicinal product. Depending on the therapeutic setting, efficacy can relate to onset of effect, maintenance of effect or durability of response and longer-term clinical outcomes. To balance against efficacy, toxicities arising from short-term and long-term use should be quantified in terms of frequency, severity and duration. Selecting an appropriate dose and posology for the target population is critical to ensuring a positive risk-benefit balance.

In general, development of medicinal products proceeds with non-clinical and clinical studies designed prospectively based on evidence that is accumulated in respect of mechanism of action, PK, PD or clinical efficacy. Evidence generated in one source population may be sufficiently relevant to another target population, that it can support subsequent development in that target population.

In consequence, the evidence needed to address the scientific questions that are important for marketing authorisation in the target population might be modified based on what is known for other populations, to focus on addressing relevant identified gaps in knowledge. Requirements for evidence generation in the target population will be a continuum, ranging from identification of an appropriate posology for the target population and quantification of a PK/PD relationship through to a full clinical development in the event that no extrapolation is possible.

It is, therefore, essential to take full advantage of existing information about the disease, the drug and the populations studied when planning and evaluating clinical studies in children. A more targeted generation of evidence should help to ensure that children only participate in clinical trials with specific objectives that further the scientific understanding of a medicinal product for use in children and address the requirements for regulatory decision-making.

A decision to extrapolate to children will carry more or less uncertainty depending on disease and drug characteristics, and the understanding thereof. In some cases extrapolation will not be justifiable where the disease is completely different in children or selected age subgroups compared to adults (e.g. neonatal disease) or the understanding of the drug's pharmacology is insufficient. In other cases it would be unethical not to extrapolate since the understanding of the disease and drug pharmacology is so well established (e.g. when a certain exposure leads to the same clinical outcome in adult and children, such as in HIV, and for some antibacterial agents).

Frequently, the knowledge of the disease and the drug is somewhere in between these extremes. The decision to extrapolate will rely on knowledge about the disease as well as understanding of the clinical pharmacology of the drug. Whilst some of this knowledge might be elicited through expert clinicians and clinical pharmacologists, various quantitative methods also exist that may be applied to support extrapolation. Objective quantification on the extent to which evidence from a source population are relevant to a target population form a more reliable basis to construct an extrapolation exercise and a better platform for discussion between regulator and developer.

Having identified the scientific questions relevant to obtain a marketing authorisation and the extent to which extrapolation can be used to address these, specific objectives for studies in children can be defined. Study objectives within an extrapolation plan might differ from objectives in studies that aim to establish clinical efficacy based on clinical outcome variables. For example, pivotal evidence in an

extrapolation plan might be based on matching exposure between the source and target population or precisely quantifying an exposure-response relationship. Additional approaches to optimise drug development in children might be employed including less common statistical and pharmacometric methods. Regardless of the complexity of the methodological approach, sound application and interpretation of results requires multidisciplinary collaboration.

2. Scope

This reflection paper aims to provide guidance to applicants and assessors on the main regulatory requirements that are expected to be met for the evaluation of extrapolation approaches in development of medicines for children. However, indicating preferences for the use of particular quantitative methods to address specific objectives of paediatric development is not within the scope of this document. The principles outlined should encourage further exploration of potentially suitable methods for specific situations, and choice of strategies should be justified.

Applicants are encouraged to discuss extrapolation prospectively with regulatory authorities, considering the potential for future extrapolation exercises even when designing studies to support initial MA in a source population.

While the focus is on extrapolation for paediatric medicines development, the underlying principles may be extended to other areas.

3. Legal basis and relevant guidelines

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, all other pertinent elements outlined in current and future EU and ICH guidelines and regulations especially those on:

- ICH E11 and ICH E11 (R) 1: Clinical Investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99);
- Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation;
- Guideline on the role of Pharmacokinetics in the development of medicinal products in the Paediatric Population (CHMP/EWP/147013/2004);
- Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005);
- Guideline on the investigation of medicinal product in the term and preterm neonate (EMEA/267484/2007);
- Guideline on the need for non-clinical testing in juvenile animals on human pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005).

4. General considerations

Extrapolation is based on information in the source population (e.g. adults and/or children) being relevant to the target population (e.g. other paediatric population), in a way that can be quantified and used as a basis for further development. For example, the influence of factors that determine exposure, such as body size and organ maturation, can be investigated in situations where the PK is assumed to be predictive of a PD response. Quantifiable links between population characteristics (body size, age and maturation), drug exposure (PK), pharmacodynamic response (PD) and clinical efficacy become, in this example, the foundation for the extrapolation concept (see further below).

Having identified the scientific questions of interest for a development targeting a marketing authorisation, the **extrapolation concept** can be developed through quantitative synthesis and comparison between source and target populations. The extrapolation concept will include those scientific questions of interest that can be addressed on the basis of extrapolation. Other scientific questions of interest, where information from the source population is of no, or negligible, relevance still need to be addressed elsewhere in the development plan but can be handled outside of the extrapolation concept and plan. The extrapolation concept will identify not only gaps in knowledge that need to be filled and assumptions that need to be investigated for an extrapolation to be valid but also important aspects of the concept where gaps in knowledge do not exist and hence further data need not be generated. For example, if the relationship between a particular PK metric or PD response and efficacy is well quantified and is applicable to the target population, no relevant gap in knowledge exists and further data to confirm that relationship will not need to be generated. Important uncertainties and assumptions should be addressed based on specific study objectives and designs that are documented in the **extrapolation plan**. If the objectives of these studies are met the extrapolation concept might be considered valid. Otherwise the extrapolation concept and plan should be revisited. **Mitigation of uncertainty and risk** for residual uncertainties may continue to be addressed post-authorisation. It is important to seek regulatory agreement on an extrapolation concept and proposed extrapolation plan before studies are conducted, and again for important changes to the concept or plan as data in the target population emerge. The extent to which extrapolation may be applied may differ between age groups of the paediatric population.

When extrapolation from the target population can be employed across a range of age subsets, studies should particularly focus on those age subsets or disease subsets where gaps in knowledge are greatest (e.g. infants and neonates) and extrapolation requires the most support. Interpolation to other paediatric age subsets might then be justified.

The clinical studies will need to be tailored accordingly and additional clinical studies with different objectives would be required in age subsets where use of extrapolation cannot be supported. It may be beneficial to introduce specific clinical study design elements in trials of the adult population (e.g. additional timepoints, dose-levels or biomarker) to inform and strengthen a future extrapolation concept for development in children.

If differences in disease, drug pharmacology and/or clinical response can be quantified with sufficient precision, an extrapolation plan might be constructed based on the relationship between dose, exposure and pharmacodynamic response or efficacy. Equally the understanding of disease and pharmacology might be such that a mechanistic model can be developed. Where gaps in understanding of disease or pharmacology are greater, the use of existing knowledge from source population and clinical data in the source population might still be relevant to inform and optimise the development required in the paediatric population. If so, the overall quantity of clinical data to be generated in the target population might be reduced without compromising the level of confidence in conclusions.

The development programme in a target population will be driven not only by the content of an extrapolation plan but also by rationale drug development (e.g. study of lower dose levels to confirm safety might be required in circumstances where the potential incidence, or degree of toxicity is of particular concern before administering a dose that predictions indicate likely to be efficacious). In some development programmes the studies required according to an extrapolation plan

Evidence for efficacy and risk-benefit generated within the framework of extrapolation should result in the same quality of regulatory decision-making as that based on self-standing clinical trials. Assessments of efficacy and benefit-risk are often associated with uncertainties and this will also be the case when the clinical data generated in the target population are to support evidence of efficacy through extrapolation. It is possible that uncertainties underlying the extrapolation concept will not be

fully resolved by the time of marketing authorisation despite a conclusion of efficacy or positive risk-benefit. In this case these might be addressed through additional follow-up data generated post-authorisation.

5. Proposed Framework:

5.1. Extrapolation concept: synthesising evidence to identify gaps in knowledge and to make predictions for effects in the target population

The extrapolation concept should build upon relevant available data from source (adult or other paediatric populations) and target populations. All relevant data should be systematically reviewed to identify potential differences between characteristics of the source and target populations e.g. body size, age and maturation, drug exposure (PK) and their relation to pharmacodynamic response (PD) and clinical efficacy.

Gaps in knowledge should be identified as uncertainties to be addressed in the extrapolation plan. The strength of existing knowledge and how much weight can be attributed to this is a combination of actual data and value judgements. (Semi) quantitative methods that summarise value judgements can facilitate their integration with actual data.

5.1.1. Evidence synthesis and predictions

The similarities and potential differences between source and target population should be assessed using mechanistic and / or empirical approaches. The choice of the approach to be used should be based on the available knowledge and the existing uncertainties about the disease and drug effects in the source and the target populations.

In order to develop explicit predictions, quantitative methods should be applied, to the extent possible, to each of the following:

- Disease manifestation and progression: quantitative synthesis of natural course of disease data or disease models can be used to characterise differences between source and target populations.
- 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.
- Characterization of PK and PD: modelling relevant data (in-vitro, animal and clinical data) using for example empirical population PK/PD, systems pharmacology or mechanism-based approaches to investigate or predict the drug exposure (PK), the relationship between PK and pharmacodynamic response (PD) and clinical efficacy, and the impact of potentially important covariates (e.g. body size and organ maturation).

When mechanism-based models are used, they should be qualified for the intended use. Expectations for qualification of a model used only to predict response in the target population to inform the design of a clinical study will differ to those for a model proposed for use to reduce or to replace prospective data generation.

When more empirical approaches are used, appropriate statistical methods can be applied for comparison and for quantification of uncertainty (precision of estimated effects) between groups (e.g. a Bayesian framework or model-based meta-analysis).

Quantitative approaches to elicit expert interpretation to integrate the available information with expert judgement could be considered as part of the extrapolation exercise although there is limited regulatory experience in the application of such approaches.

The evidence synthesis (qualitative and quantitative) should result in explicit predictions for drug effects in the target population reflecting the impact of differences in e.g. drug exposure (PK) and pharmacodynamic response (PD) in the target population as compared to the source population in response to the treatment. Structured documentation should be provided, detailing gaps in knowledge and including an assessment of the impact of identified uncertainties on the predictions (see 5.1.2).

Safety information from the source population (e.g: other paediatric population for another disease or from other drugs with the same of mode of action) may be used to predict risks related to the mode of action of the drug and related to dose. However considering that risks related to growth and maturation cannot be extrapolated from adults, generation of new safety data are often likely to be needed in the target population to address unexpected (age-specific) risks.

5.1.2. Assumptions and uncertainties in making predictions

The reliability of the prediction(s) must be determined to enable decisions on the objectives for the extrapolation plan. To allow this, a structured and transparent approach should be taken towards documenting and evaluating the impact of potential sources of uncertainty and important assumptions about the predictions made, and the consequent inferences.

It is inevitable that there will be uncertainty coming from the quality, completeness and relevance of source data and the assumptions made in constructing the extrapolation concept.

Uncertainties in using the source data to develop specific predictions in the target population could, for example, be due to the (lack of) consistency, coherence, and volume of evidence, complexity and high biological variability, measurement error and variability or lack of understanding. Assumptions can be divided into those that can be addressed through available evidence and those that will be based on data that will be obtained in future studies (whether in the source or in the target population). Assumptions are usually structured around five main areas, clinical pharmacology (the compound and the patient), physiology, disease considerations, existing data, as well as the mathematical and statistical assumptions underpinning any quantitative model.

Scenario analysis including sensitivity analysis can be useful to investigate the impact of the identified assumptions and uncertainties in the extrapolation concept, such as what is known and not known about the medicinal product, the paediatric formulation, clinical pharmacology, disease progression, and clinical response. Scenario analysis based on ranges of plausible values or relationships for each assumption or uncertainty can help to identify which aspects are critical for the extrapolation plan, specifically those where inference is not robust to different scenarios examined. This in turn can identify those assumptions and uncertainties that needs to be explicitly addressed before marketing authorisation either before initiating the extrapolation plan or as part of the plan, and which can be addressed post-approval. The scope of the extrapolation (in particular whether the plan is to reduce or replace clinical studies) should be considered when determining the plan for assessing the impact.

5.2. Extrapolation plan

An agreed extrapolation concept will outline not only gaps in knowledge that need to be filled and assumptions that need to be investigated but also important aspects of the extrapolation that are not required to be further investigated in the target population. The extrapolation plan on the other hand will address the specific scientific questions that remain to be answered through clear study objectives. In accordance with the requirements to obtain a marketing authorisation, regulatory decision making will be made on the totality of evidence: that which is available and agreed to be relevant from the source population and that which is generated in the target population.

The extent to which data will need to be generated in the target population lies on a continuum and may differ between age groups of the paediatric population. Each extrapolation concept and plan will be individual but some general scenarios can be outlined for illustration. For example, where it is known that a particular exposure will achieve therapeutic efficacy, critical gaps in knowledge might relate only to establishing adequate dosing in paediatric patients by matching exposure levels (see also PKPD studies in the extrapolation plan). Examples of this could be some antibacterial agents. Alternatively, when there is confidence in the similarity of disease such that therapeutic efficacy can be inferred from obtaining a target pharmacodynamic response, approaches that confirm the PKPD relationship in the target population could be appropriate. In both scenarios, adequate studies will be needed to establish the dosing recommendations (see also PKPD studies in the extrapolation plan). Finally, when there is remaining uncertainty on the predictability of the PD marker(s) on the clinical response, there might still be a need to generate at least some efficacy (and safety) data in the target population. Appropriate methodology must be used to support the proposed reduction in the amount of clinical data that need to be generated (see also Therapeutic Studies in the extrapolation plan).

The measures proposed in the extrapolation plan should be as detailed as possible in their pre-planning and clearly documented. When differences between source and target population require investigation across age subsets but the clinical endpoint, biomarkers or surrogates in adults can't be used in all paediatric age subsets (e.g. 6 minute walking test), it may be prudent to initiate the validation of endpoints for use in children during the trials in adults. It may be possible to use surrogate or intermediate clinical endpoints for studies in the extrapolation plan, providing that they have been validated and that they account for the physiologic developmental changes in the paediatric population. If an endpoint is an accepted surrogate, there is no obligation to confirm clinical benefits.

The initial extrapolation plan should allow for refinement given emerging information (e.g. natural history or epidemiological data relevant to similarity or differences in disease, PK, PD and clinical response) during the development program. If the initiation of paediatric studies depends on data from an initial study or qualification measure, these preceding studies should be outlined as interim or exploratory steps in the extrapolation plan.

Evidence generated should feedback into the extrapolation concept and the underlying assumptions should take account of new data and be reviewed before initiation of subsequent paediatric studies. The extrapolation plan should encompass all studies that contribute to extrapolation, including those to be conducted post-authorisation studies.

The benefit of a staggered approach across age groups, due to safety concerns or the need to have PK and PD information in older children before enrolling younger children, should be balanced against the need for timely access to a medicinal product even for the youngest age groups of the paediatric population.

5.2.1. Design of studies in the extrapolation plan

The objectives of studies in the extrapolation plan should be tailored to their role in the extrapolation concept. Objectives would differ between a study that is designed to explore safety and dose finding in order to inform the design of subsequent efficacy and safety studies in the target population and a study that aims to demonstrate similar exposure or PK/PD relationship between the source and the target population.For the latter, it is important to consider the extent of information required, translated into justified and pre-defined criteria to evaluate the success of the study. For example, the magnitude of differences in exposure to be excluded in order to conclude that exposure is similar in the source and target populations.

Sections 5.2.1.1 and 5.2.2.2 provide general recommendations on the design of paediatric studies when extrapolation strategies are considered.

5.2.1.1. Pharmacokinetic studies and Pharmacokinetic / pharmacodynamic Studies in the extrapolation plan

PK and/or PD data will almost always need to be generated as part of the extrapolation plan. Replacement of PK or PKPD studies with model predictions for dose selection purposes is normally not acceptable, as there still are gaps in existing knowledge of paediatric PK and PKPD. For example, gaps in knowledge related to organ maturation and ontogeny of enzymatic and transport functions particularly in the youngest age groups of the paediatric population are sources of uncertainties and can affect the reliability in the predictions.

As described above (5.2.1) clinical PK or PKPD investigations may serve different purposes within an extrapolation plan. Clinical PK/PD studies that can be required as elements of a plan include:

- Exploratory PK/PD dose ranging or dose finding studies in one or several paediatric age ranges;
- PK or PK/PD studies that aim to confirm inferred exposure levels in one or several paediatric age ranges.

Depending on the PK and/or PK/PD study objectives various designs, different metrics of interest and decision criteria can be considered. Every effort should be made that the studies are designed and powered to meet their objectives. Reference is made to the "Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population" for general guidance on PK/PD investigations. Methods for study design optimization such as FIM-based methods, clinical trial simulations and adaptive study design should be used as appropriate.

The choice of exposure metric(s), the PKPD relationship and criteria by which similarity between source and target populations is assessed must be justified. Criteria can be developed as part of the extrapolation concept, by thorough dose finding in the source population and description of the exposure-response relationship or can be developed through the extrapolation plan. For studies that aim to confirm assumptions of the extrapolation concept, the success criteria will need to be pre-specified.

For example if based on the extrapolation concept the exposure-response relationship is established to be identical in adults and children, the objective of the PK study should be to identify the dose in different age groups that match the PK exposures that were related with clinical efficacy in adults. Still the relevant exposure metrics of interest, e.g. AUC0-t, Cmax, and the acceptable equivalence margins should be pre-specified. Ideally the study should be powered to meet a pre-specified and justified equivalence margin. Even in this simple scenario it may be impossible to get comprehensive evidence in all age groups. For example there may be not enough infants to confirm a dose that gives rise to equivalent exposure in this population. Systems knowledge on organ and enzyme maturation effects on PK could help reduce uncertainties in this particular subgroup. An additional objective of the PK study in this subgroup may be to collect data to exclude major deviations from our PK understanding coming from systems knowledge. The metrics, design and the power of study should be adapted accordingly.

Design considerations: There is a wide spectrum of approaches and study designs that may be acceptable to explore or confirm an adequate dosing rationale or assumptions of the extrapolation concept. Different age cohorts can be enrolled in parallel or sequentially when justified, i.e from older to younger children, in paediatric PK or PKPD studies. Usually the dose regimen tested in children is the one predicted to give similar exposure or response to adults. However, more dose level may need to be tested in children if the exposure response relationship is not known or cannot be assumed to be the same as in adults. Measures to handle unanticipated differences in PK/PD should generally be factored into the study design. Interim analysis or real time PK/PD evaluation may also be used to adjust doses in children.

The PK/PD studies may be stand alone studies or be conducted as part of a confirmatory efficacy trial. In either case, it should be ensured that they are optimally designed for their purpose.

5.2.1.2. Therapeutic Studies in the extrapolation plan

The objective of the therapeutic study might be to exclude any large discrepancy between the predicted and observed efficacy and the success criteria should reflect this aim accordingly. For other extrapolation plans, the generation of efficacy data will be specified as the pivotal evidence, perhaps at a nominal significance level that is higher than the conventional 5% two-sided level to reflect the justified use of information from the source population. The following design aspects should be considered carefully:

Sample size: studies should be adequately powered based on clear objectives aligned to the extrapolation plan. If the required sample size is not feasible because of constraints such as rarity of disease, target population or ethical considerations this should be addressed separately and not by artificially amending study objectives, criteria for success or information to support the sample size calculation (e.g. the anticipated variability).

Once a reduced sample size supported by extrapolation of data from a source population has been justified, this should be translated to the prospective study design through appropriate statistical approaches. Examples of approaches could be using a higher nominal significance level than the usual 5% two-sided, widening a non-inferiority margin or using Bayesian methods 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. Quantitative justifications should be provided for the extent to which the evidence generated in the target population is reduced. Uncertainties in borrowing information from external data sources should be reflected in the extent to which reductions in sample size are proposed. Borrowing information to such an extent that data generated in the target population would not be informative cannot usually be supported.

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.

If there are 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). It might then be preferable to regard these as separate age subsets in the extrapolation concept and plan.

Choice of control group: randomised, controlled studies, double-blind where feasible, are preferable in order to provide an estimate of the active treatment effect. Estimates of treatment effects relative to control might form a better basis for comparison between the source and the target population than absolute changes from baseline within two different patient populations.

The formal incorporation of historical controls is possible, but inherently introduces further uncertainties to such comparisons. The historical controls should match the treated paediatric population as closely as possible.

Endpoints: endpoints for studies in the extrapolation plan should be aligned with the extrapolation concept. For studies with an intention to extrapolate efficacy from adults to children where using PK as a bridge would not suffice, the primary endpoint that may predict outcome in confirmatory PK/PD trials should be a clinically meaningful endpoint that directly measures how a patient feels, functions, or survives. Studies should ideally include outcome measures applicable to young children that should correlate with clinical markers of disease severity and may also predict outcome. If there are no

clinical trial endpoints, including biomarkers or surrogate endpoints, applicable to both the source and target populations, the use of extrapolation based on clinical data becomes more complicated. Where it is necessary to investigate clinical efficacy in the target population, endpoints chosen should be clinically relevant to the paediatric population and the research question, and should be sufficiently sensitive to enable the study to detect a clinically relevant difference between treatment groups if one exists. Sensitivity of the endpoint is especially important if the patient population is limited by feasibility constraints. As continuous scales are often the most sensitive to detect true differences between predicted and observed efficacy, they may be more suited to provide a meaningful basis for extrapolation than those based on responder rates alone.

5.2.2. Validation of the extrapolation concept

If the data generated from the studies specified in the extrapolation plan are able to address the gaps in knowledge and assumptions identified in the extrapolation concept, according to the agreed criteria for success, the use of extrapolation to support regulatory decision making can be considered valid.

If the data generated do not confirm the extrapolation concept, e.g. the predictions made for similarity in PK or, PK/PD relationships, or for efficacy, cannot be confirmed, the extrapolation concept needs to be updated (see section 5.2) to reflect the data generated and the ability to extrapolate should be reconsidered. Consequently, according to the remaining uncertainties, the extrapolation concept and plan to generate more data in the target population or part of the target population should be re-assessed.

5.3. Mitigation of uncertainty and risk

A formal, structured plan to mitigate risks and address key uncertainties during development and in the post-authorisation setting should be proposed as part of the extrapolation plan and updated in response to the results of the studies conducted.

If a high degree of confidence in an extrapolation concept exists, this will inevitably result in less data being generated in the target. The data generated in the target population may not fully address all uncertainties and assumptions underlying the extrapolation concept by the time of marketing authorisation. Additional data, generated post-authorisation, may be necessary for example, to document longer-term efficacy outcomes.

5.4. Submission and reporting of the extrapolation exercise

When developing an extrapolation concept and plan, it will be necessary to provide an overview of the existing available data and planned clinical data from the source and target populations. The source data should be the basis for the description of evidence synthesis and investigation of differences between source and target population. It should lead to a clear description of the extrapolation concept, and the associated gaps in knowledge (uncertainties) and assumptions.

When model-informed approaches are used a modeling and simulation plan, including the approach to qualifying or evaluating a model for a specific purpose of use, should be submitted and discussed with regulators. All pertinent information regarding the model building and evaluation should be pre-specified as part of the extrapolation plan, including sources of data, study size and duration, relevant covariates, number of samples and sampling times. The relevant Modelling and Simulation reports should be submitted following the format proposed in relevant guidance documents.

Based on the extrapolation concept, the specification of key scientific questions of interest and specific trials listed with objectives, key design elements and criteria for success that can inform the size of the

trial should be presented using the extrapolation framework in regulatory procedures at e.g. PDCO, SAWP or CHMP.

Once a test or trial that is part of the extrapolation plan has been completed, a report may be submitted as a complement of the Clinical Study Report, integrating the new information with existing knowledge to update – if appropriate – the extrapolation concept and plan.

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			Pharmacology Drug disposition & effect	**Disease manifestation & progression**	**Clinical response to treatment** Efficacy & safety
SOURCE POULATION Adults and/or paediatric	**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 subgroups		**Prediction**	Predict doses to achieve - similar exposure, or - similar PD effect, and - acceptable safety per paediatric subgroup	Describe/predict differences in natural course of disease progression by paediatric subgroup	Given similar drug exposure or PD response, predict degree of differences in - efficacy - safety - benefit-risk balance by paediatric subgroup
			➢ 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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