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Committee for Medicinal Products for Human Use (CHMP)

Structured guidance on the use of extrapolation

Contents

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1. Introduction and scope

This document reflects practical aspects on how to use the published reflection paper on the use of extrapolation of efficacy and safety data in the development of medicines, with a focus on paediatrics (EMA/189724/2018). The extrapolation exercise is divided into the extrapolation concept and the extrapolation plan.

This document intends to provide structured guidance to applicants/marketing authorisation holders on how the extrapolation concept and extrapolation plan should be presented, using the structure below. It also intends to support regulatory assessments of extrapolation proposals.

It is recognised that extrapolation might have a different relevance for each development programme (e.g. overall possibility to extrapolate; applicability only to exclusive paediatric sub-groups such as adolescents; differences in study designs outlined in the extrapolation plan based on the level of existing evidence). The comprehensiveness of extrapolation applied and its relevance for assessment of benefits and risks is a result of the level of evidence available for a specific substance at a given time and the remaining uncertainties subsequently identified. This can be different for individual therapeutic areas (e.g. use of extrapolation for medicines used for the treatment of epilepsy or for antimicrobials for which precedents exist), but might also alter in view of the novelty of a compound (e.g. first in class, where the level of knowledge is usually low). The intention to extrapolate safety implies a separate discussion which should take into account the level of existing evidence for the individual drug and/or for the class (if applicable), particularly in relation to the immaturity of drug metabolising enzymes and/or transporters or to effects on developing organs (e.g., fluoroquinolones and cartilage damage in juvenile animals).

If it has already been concluded that extrapolation is scientifically justified (e.g. as per disease specific EMA guidelines as precedents exist), then this should be reflected adequately, but might not necessitate further use of this guidance template.

Lastly, it is emphasised that extrapolation is an evolving methodology. Therefore, this guidance is not exhaustive and new knowledge through emerging data or new approaches should always be reflected upon.

2. Extrapolation concept

This should include a discussion on the possibility for extrapolation to support development which should be focused on limitations and uncertainties in any relevant target population, taking into consideration the 'Reflection paper on the use of extrapolation in the development of medicines for paediatrics' (EMA/189724/2018). The table structure below should be used when providing the respective reflections and data.

Expected clinical response to treatment in proposed target population based on available knowledge on pharmacokinetics (PK)/pharmacodynamics (PD), efficacy and safety	
Summary of existing evidence and gaps of knowledge	The main purpose of an extrapolation exercise is to identify the data required to demonstrate that the therapeutic response in the target population is expected to be similar to the response established in adults (and/or other paediatric sub-sets within the same or different indications), so that a stand-alone demonstration of efficacy in the target population is not needed. The extrapolation concept summarises the existing evidence and the gaps in knowledge that need to be filled in order for expectations on the effects of treatment in the target population to be formulated. The evidence required to fill these gaps is summarised in the extrapolation plan (see below). A number of assumptions need to be outlined to support this, some rely on available data or physiological/pathophysiological/pharmacological principles; others need to be confirmed by dedicated studies. Other assumptions cannot be verified at a given time point and the associated risks from this uncertainty have to be quantified and considered when concluding on the validity of the extrapolation concept. The application submissions/assessment report(s) should at the very least contain a discussion on the following points. ***Disease similarity*** A discussion on disease similarity between the source (e.g. adult) and target population (e.g. paediatric) should be included in terms of manifestation, severity and phenotype, clinical course and potential resolution supporting the use of extrapolation. Discuss also if the pharmacological target is playing a different role across populations (e.g. are there differences in cellular target expression levels)? Have age-related differences in the activity/relevance of the pharmacological target been identified? ***Response to treatment*** (issues to be considered – not exhaustive) Is there evidence to support that the response to treatment is the same in adults and paediatric patients? Is there any evidence on the use of a medicine from the same class in the different age subsets?

Expected clinical response to treatment in proposed target population based on available knowledge on pharmacokinetics (PK)/pharmacodynamics (PD), efficacy and safety	
	Will the data generated in adults (or older paediatric subjects) address the main uncertainties with regard to response to treatment in the target population? How will this be compared? Based on the mechanism of action, are there developmental factors and/or functions (e.g. growth, immunology, sexual or cognitive development) to be considered with respect to the expected response to the treatment? Prior treatment history: are paediatric and adult patient populations similar in terms of previous treatments/treatment response? Are the clinical end-points used comparable between the relevant populations (e.g. between adults and children and/or between different paediatric age subsets)? Maintenance of effect: are there differences in spontaneous improvement without treatment and/or timing of response to treatment? Concerning safety, considerations should be made about the level and relevance of the existing knowledge of the specific drug and/or drug class based on non-clinical and clinical data, including other indications (if available and applicable), particularly in case there is evidence that there may be deleterious effects on developing organs. Are there potential long-term treatment safety issues related to developmental changes (e.g. risk of clinical sequelae, or worse outcome expected due to increased vulnerability)? ***Pharmacokinetic and pharmacodynamic aspects*** Ontogeny: are the ADME pathways involved no longer under maturation in the target population so that relevant differences are to be expected in absorption, distribution, metabolism and excretion? A discussion on anticipated differences in pharmacokinetic properties between the target and source population should be presented. Are data on exposure-response relationship available in adults and children or are there plans to generate it? Description of the relationship between exposure and response (e.g. is the exposure/response or PK/PD relationship investigated or defined, and have any covariates been identified; e.g. age, body-weight, body surface area [BSA])? Are there maturation and development parameters known leading to difference in exposure response in the relevant age subsets, e.g. age-related differences in immunoglobins, receptor expression? Is the therapeutic window wide/narrow? Have PD parameters/biomarkers been identified with respect to the drug's mode of action in the relevant population?

Expected clinical response to treatment in proposed target population based on available knowledge on pharmacokinetics (PK)/pharmacodynamics (PD), efficacy and safety	
Relevant risks and remaining uncertainties	Discussion here should be structured in a similar way as the evidence on the existing knowledge is presented. What are the uncertainties that cannot be fully resolved based on the available data/knowledge listed above? Can these be addressed by studies included in the extrapolation plan? If not, can the risks be quantified and are they considered manageable? ***For Paediatric Investigation Plan (PIP) considerations only*** Is there a risk that an age appropriate formulation (e.g. due to different formulation technology and/or excipients) or the use of an interim formulation (resulting in lack of PK/clinical data with the final age appropriate formulation) may require additional bridging considerations? How relevant is existing non-clinical and clinical information in support of the extrapolation of PK and/or PD, and/or safety? Can additional non-clinical/ in-vitro studies (e.g. on the presence of the target) be used to mitigate the risk?
Conclusion	***Based on the above reflections, a conclusion should be drawn on the general acceptability of using extrapolation and remaining uncertainties, outlining the necessary studies to be conducted in the extrapolation plan to adequately address the latter (see below under point 3).***

3. Extrapolation plan

The extrapolation plan should elaborate on how the remaining uncertainties described in the extrapolation concept are going to be adequately addressed prospectively.

To support development in proposed indication	
Define source and target paediatric population (e.g. different age subsets) and the specific study objectives. A summary of all proposed studies (and its results) should be presented, reflecting how it adequately addresses the remaining uncertainties with regard to PK/PD, response, efficacy and safety.	
Objectives of the extrapolation plan	The objectives should be specific and define how proposed studies (in the source population) will address the uncertainties identified in the extrapolation concept (e.g. to support the assumptions concerning a paediatric dose, differences in efficacy in the respective paediatric population). ***For PIP considerations only*** From a PIP perspective it should have quantitative outcome (based on adequately pre-defined criteria), e.g. to demonstrate similar efficacy outcomes in the two populations (acceptance criteria to conclude that the efficacy in the two populations is similar should be pre-defined.) Present data and analysis supporting the assumption that the outcome of treatment is likely to be similar between the target paediatric population (define the age-groups) and the source population (defining adults/adolescents/older paediatric age groups).
Methodology	The methodology should reflect the questions being answered. If efficacy data is not to be generated, one example could be to compare pharmacokinetic data in adults and children (i.e. PK bridge). If efficacy data are required, one approach to the design of the study could be to generate data on efficacy using appropriate study designs but a higher nominal significance level than the usual 5% two sided, widening a non-inferiority margin or using Bayesian methods to explicitly borrow information. Alternatively, the study could be designed to confirm that the observed efficacy in the relevant paediatric populations is similar to that predicted based on the source data. Where stand-alone efficacy data are not being generated the extrapolation plan should contain a description of any planned statistical analyses to be conducted that assess the similarity (preliminary criteria for similarity should be included) in exposure, efficacy and safety between paediatric patients aged x to y years and older patients.
Mitigation of uncertainties	Where long-term follow-up studies are required to address uncertainties, high-level planning for such studies should already be considered early in the development. A proposal to mitigate residual uncertainties not addressed by the studies proposed, to join the pre-authorisation phase with the post-authorisation setting, should be outlined as part of the extrapolation plan and updated in response to the results of the studies conducted.

To support development in proposed indication	
	To further reduce remaining uncertainties, it could be considered to discuss the benefit of additional studies, or a continued follow-up of patients from ongoing studies, to address specific uncertainties related to the understanding of therapeutic efficacy and/or safety which might have more long(er) term implications on understanding the benefit-risk of a medicine.