

**Final Concept Paper
Pediatric Extrapolation**

3 October 2017

Endorsed by the Management Committee on 17 October 2017

Type of Harmonisation Action Proposed: New Efficacy Guideline under E11: E11A Clinical Investigation of Medicinal Products in the Pediatric Population

Statement of the Perceived Problem

In both the US and EU, pediatric legislation has increased the number of approved drugs with specific efficacy and safety data in labeling for pediatric populations. However, in many cases, there is still a long gap (between 7-10 years) between the initial adult approval and the inclusion of pediatric-specific information in product labeling. The use of pediatric extrapolation has advanced substantially as an approach to improve the efficiency and success of pediatric drug development. However, there is variability in the interpretation and application of extrapolation across regulatory authorities. Harmonization of methodologies and strategies to incorporate pediatric extrapolation into overall drug development plans will improve the speed of access to new drugs for pediatric patients.

The current E11(R1) concept paper recommends that more detailed guidance be developed to advance the use of pediatric extrapolation. The current E11(R1) guideline only includes a high level description of pediatric extrapolation that encourages sponsors to initiate a discussion of using this approach in regulatory interactions. Therefore, there is a need to provide more detailed guidance about how pediatric extrapolation can be used in successful pediatric product development, leading to marketing authorization.

Issues to be Resolved

This topic specifically pertains to pediatric drug development. Therefore, we propose that this guideline be considered as a stand-alone guideline under the E11: Clinical Investigation of Medicinal Products in the Pediatric Population guideline (e.g., E11A: Pediatric Extrapolation). The following topics should be addressed in this new guideline:

1. Address and align terminology related to pediatric extrapolation

This guideline would also provide a definition of pediatric extrapolation to distinguish the pediatric use of extrapolation in pediatric drug development from other forms of extrapolation in drug development.

2. Provide information on various approaches that can be utilized to support the use of pediatric extrapolation

This guideline would include approaches and tools to assess disease similarity and response to treatment in the source populations. The guideline should describe the quality and quantity of evidence needed to support the development and use of extrapolation as well as describing the level of uncertainty and assumptions underlying an extrapolation approach.

3. Discuss a systematic approach to use of pediatric extrapolation

This guideline would provide a systematic approach on the use of extrapolation in pediatric drug development, including the framework for extrapolation as provided in the draft EMA extrapolation reflection paper (2016). Differences in the application of this approach across regional authorities would be addressed and harmonised to the extent possible.

- a) Systematic assessment and synthesis of existing data, including the use of modelling and simulation (M&S) to assess relevant relationships between source and target population on several levels (PK/PD, disease progression, clinical response);
- b) Quantitative (rather than qualitative) predictions on the degree of similarity between the source and target population;
- c) Development of a framework for the potential reduction of the required evidence generated in the target population in accordance with the predicted degree of similarity to the source population;
- d) Analysis of data generated to review and revise uncertainties and assumptions.

4. Discuss study designs, statistical analysis, M&S analyses and respective methods

This guideline should provide information on study designs and statistical analysis methods used when incorporating pediatric extrapolation into a pediatric drug development plan. Discussion should include:

- a) Appropriate collection of exposure-response information in both the source and target populations
- b) Use of M&S in the planning and analysis of pediatric studies.
- c) Clinical trial designs (including pediatric-specific study design elements) appropriate to collect data to fill gaps in knowledge (e.g. informative dose-finding study designs in pediatric patients)
- d) Incorporation of appropriate statistical analysis methods, including Bayesian and other methodologies, to address uncertainties and assumptions in extrapolation approaches.
- e) Examples should be provided to illustrate essential considerations and approaches for successful planning and implementation of an extrapolation approach in pediatric drug development.

Background to the Proposal

Historically, pediatric extrapolation has been based on the assumption that there is a sufficient similarity in disease and response to therapy between adult and pediatric patients to allow for collection of different level of evidence to support approval of a product for use in pediatrics. Also, it has generally been required that additional dosing and safety information always be collected. With increased knowledge and understanding, there have been refinements in application of extrapolation in pediatric drug development over the last 20 years.

There is now more scientific and regulatory experience on the use of pediatric extrapolation. For example, the uncertainties in the similarity in disease and response to therapy between the source and target population can be viewed as a continuum rather than a specific, sufficient level that must be achieved. These uncertainties affect the confidence in assumptions made in a pediatric extrapolation plan. The availability of existing data affects the degree of uncertainty and confidence in these assumptions. Additionally, the generation of additional data in any proposed pediatric studies should address the uncertainties and confidence in these assumptions.

Quantitative approaches to the review of existing data as well as the data that need to be generated are critical in increasing the success of drug development programs because these approaches maximize the use of existing data, increase the efficiency of development programs, and limit the number of children required for enrollment in clinical trials. This guideline would address these approaches that can provide the basis for regulatory decision making.

An expert working group (EWG) was formed to revise the ICH E11 guideline, Clinical Investigation of Medicinal Products in the Pediatric Population in 2014. E11(R1) has recently achieved Step 4, and has been adopted as a final guideline by the ICH assembly. This revision includes a high level discussion of pediatric extrapolation, but a more comprehensive discussion of pediatric extrapolation is beyond the scope of the current revision. The E11(R1) EWG is fully supportive of a separate guideline (e.g., E11A: Pediatric Extrapolation) to provide more specific and detailed guidance about the use of pediatric extrapolation in pediatric drug development.

Type of Expert Working Group Recommended

The EWG should include experts in clinical pediatrics, clinical pediatric pharmacology and pharmacometrics (including modeling and simulation experts), and statistics (including Bayesian and other statistical methodologies).

Timing

It is anticipated that this guideline would take a minimum of 3 years to be developed (based on overall experience from the E11(R1) EWG).