



The role of extrapolation as basis for paediatric marketing authorization applications of medicines in the EU.

Background

Understanding the contribution of extrapolation in paediatric evidence generation.

- Generation of evidence in the paediatric population is often hampered by difficulties in conducting clinical trials.
- Drug companies obtain regulatory approval on the strategy to generate sufficient evidence to support paediatric marketing authorisation applications (PMAAs).
- Extrapolation from adult or different paediatric populations based on matching exposures can support evidence generation if:
 - ➡ Similar disease progression;
 - ➡ Similar exposure-response;
 - ➡ Similar treatment response².
- The study investigated the successfulness and efficiency of PMAAs supported by extrapolation based on exposure-matching.

Results

Extrapolation based on exposure-matching drives success, but at a cost of time (Figure 1 and 2).

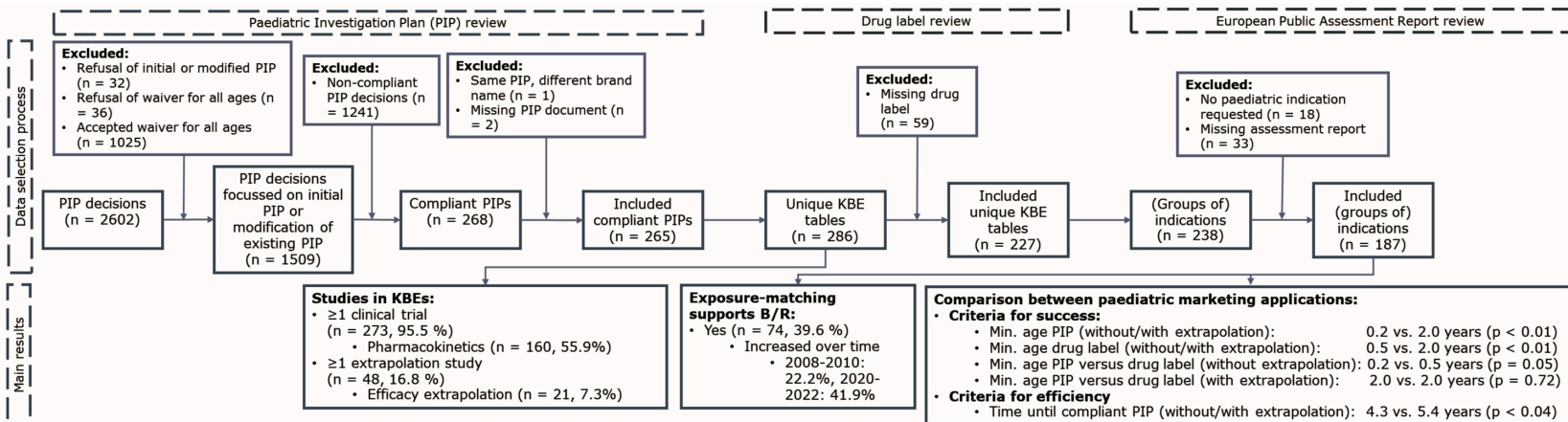


Figure 1. Flowchart of included paediatric investigation plan documents, unique key binding element tables and (groups of) indications and summary of results.

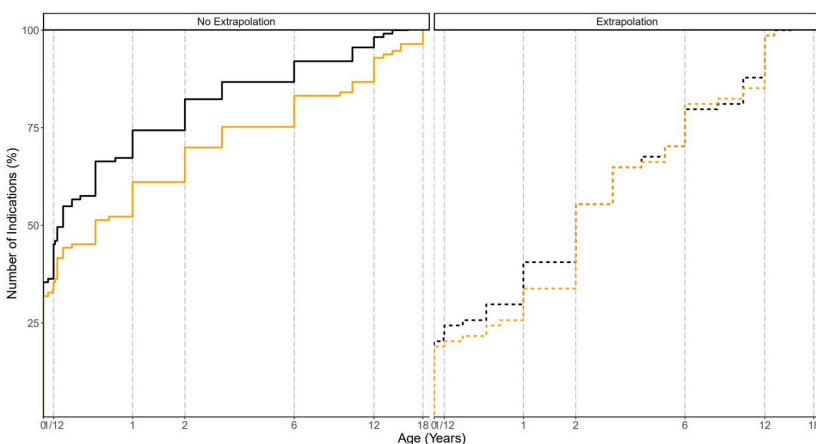


Figure 2. Cumulative number of indications vs. minimum age specified in PIP (black line) and in drug label (orange line) stratified by use of paediatric extrapolation based on exposure-matching.

References:

- CHMP. Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. EMEA/CHMP/EWP/147013/2004.
- ICH. Guideline E11A Paediatric Extrapolation. EMA/CHMP/ICH/205218/2022.
- Musumba FT, Cheung SYA, Colin P, et al. Moving toward a question-centric approach for regulatory decision making in the context of drug assessment. Clin Pharmacol Ther. 2023;114(1):41-50. doi: 10.1002/cpt.2856.

Methodology

A comprehensive analysis of regulatory paediatric drug approvals.

- Data was sourced from completed paediatric investigation plans (PIPs), drug labels, and European Medicines Agency assessment reports.
 - ➡ Key binding elements (KBEs) included extrapolation based on exposure-matching;
 - ➡ Age and body weight limits.
- Wilcoxon rank-sum tests were used to compare PMAAs that utilized exposure-matching with those that did not:
 - ➡ Time to complete drug development;
 - ➡ Restrictions on paediatric use (age and body weight).

Discussion

- PMAAs supported by exposure-matching were more successful in gaining approval for the targeted paediatric population, highlighting the effectiveness of this strategy in securing regulatory confidence for paediatric use (Figure 1 and 2).
- We found that less extrapolation is used in the youngest patients, while necessity is most prevalent in this group. The underlying assumptions of extrapolation for youngest children are prone to more uncertainties, indicating more research is necessary (Figure 1 and 2).
- To optimise exposure-matching methodologies to reduce its impact on development time, we recommend a question-centric approach for future studies, linking key research questions to the benefit-risk assessment³.



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