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Putting E11A into Practice: Extrapolation from Guideline to Application

EnprEMA Annual Conference 2025

Dominik Karres

Paediatric Medicines Office – Evidence Generation Department – Human Medicines Division

ICH harmonisation for better health

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Committee for Medicinal Products for Human Use

ICH E11A Guideline on pediatric extrapolation

Step 5

Transmission to CHMP	8 March 2022
Adoption by CHMP	24 March 2022
Release for public consultation	06 April 2022
Deadline for comments	06 August 2022
Final adoption by CHMP	25 July 2024
Date for coming into effect	25 January 2025

Paediatric development scenario

Development plan proposal

Single arm trial using **extrapolation** approach; supported by M&S and Bayesian statistics

Clinical Foundation

What do we know about the disease in context of the MoA across populations; what are the differences and uncertainties - **extrapolation concept** – which we need to address in the **extrapolation plan**

Quantitative Tools

M&S, Bayesian statistics, and **RWD** leveraged to fill knowledge gaps and reduce uncertainties.

Regulatory Assessment

Starting point: Is disease similarity sufficiently established? Do we have clarity where we have differences/ i.e. uncertainties. Can we address those **remaining uncertainties** sufficiently by single arm trial, supported by the proposed model and statistics?

Understanding the context of use of the model and the Bayesian statistics is key!

This requires **multidisciplinary discussions**

E11A implementation ⟷ Assessment processes

Concept:
What do we know about factors influencing disease, drug pharmacology, response to treatment, safety across populations

↓

Plan:
Agree to study design(s) which address these uncertainties

↓

New additional data

↓

Presentation of completed plan/ results:
Evaluation of data in context of the concept

PIP/SA submission:
Concept presented;
adequacy of use of extrapolation assessed

↓

PIP agreement:
PIP studies = **Plan**

↓

Additional data (from PIP studies or elsewhere)

↓

PIP study/ies completed - **CHMP submission:**
Reporting, analysing, interpretation in context of **pre-specified success criteria**

Iterative rounds as needed – **SA, PIP modifications**

Implementation activities – three pillars

Capacity Building

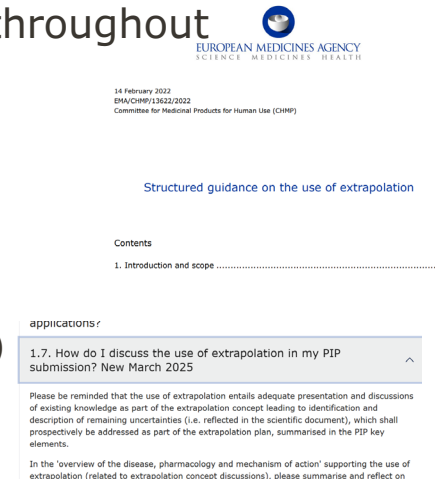
Build and strengthen multi disciplinary expertise across the **regulatory network** through a **temporary Operational Expert Group under MWP** (PDCO/SAWP/MWP/CHMP). Promoting **change management** and **avoiding silos** across disciplines and processes

Process Enhancement

Adequate **reflection** in **scientific documents** to support both industry and assessors, from preparation of **PIP, SA** and **MAA** submissions to their assessment, ensuring clarity and consistency throughout the process.

Building on:

- Published structured guidance *
- PIP scientific document (Q&A published on EMA website**)
- PIP opinion template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Structured guidance on the use of extrapolation

Contents

1. Introduction and scope 2

applications?

1.7. How do I discuss the use of extrapolation in my PIP submission? New March 2025

Please be reminded that the use of extrapolation entails adequate presentation and discussions of existing knowledge as part of the extrapolation concept leading to identification and description of remaining uncertainties (i.e. reflected in the scientific document), which shall prospectively be addressed as part of the extrapolation plan, summarised in the PIP key elements.

In the 'overview of the disease, pharmacology and mechanism of action' supporting the use of extrapolation (related to extrapolation concept discussions), please summarise and reflect on

Knowledge Dissemination

e.g. learning and experience sharing, Q&A development, EU NTC activities, publications *** and conference presentations.

* https://www.ema.europa.eu/en/documents/scientific-guideline/structured-guidance-use-extrapolation_en.pdf
** https://www.ema.europa.eu/en/human-regulatory-overview/research-development/paediatric-medicines-research-development/paediatric-investigation-plans/paediatric-investigation-plans-questions-answers
*** https://bpspubs.onlinelibrary.wiley.com/doi/epdf/10.1111/bph.17396

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Expert network input

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This requires **multidisciplinary discussions** **and all experts involved to understand how regulators assess and implement use of extrapolation**

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Thank you

Dominik.Karres@ema.europa.eu

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