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EMA extrapolation framework

Extrapolation workshop 2016-05

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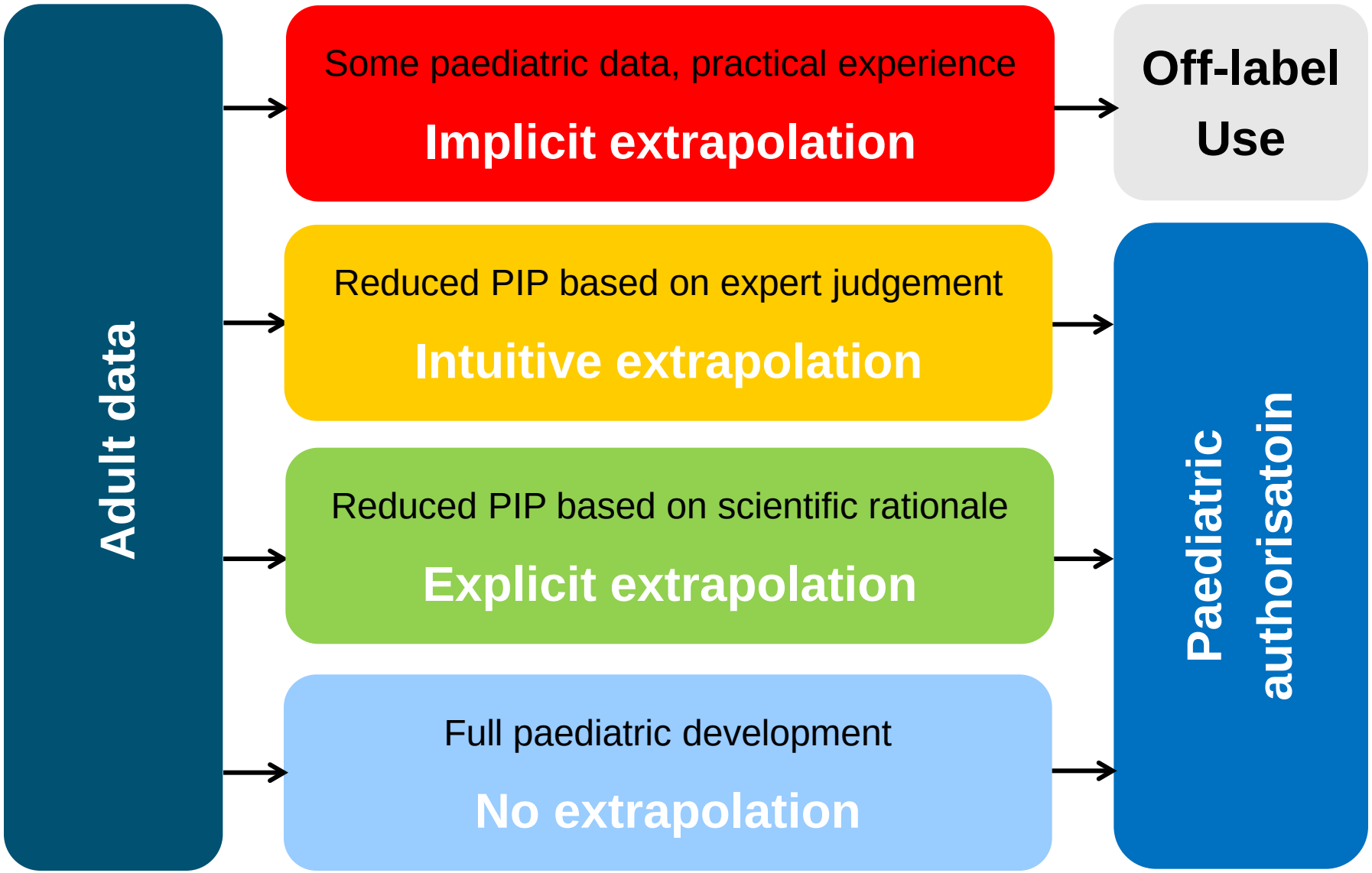
Evidence base for medicine use in children



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Reflection paper on extrapolation of efficacy and safety in paediatric medicine development

Draft

Draft agreed by Biostatistics Working Party	March 2016
Draft agreed by Modelling and simulation group	March 2016
Draft agreed by PKWP	March 2016
Draft agreed by Scientific Advice Working Party	March 2016
Draft Adopted by PRAC	17th March 2016
Draft Adopted by PDCO	31st March 2016
Draft Adopted by CHMP	31st March 2016

Keywords	Paediatrics, extrapolation, medicine development, biostatistics, modelling and simulation

Extrapolation definition

Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), …, to make inferences for another subgroup of the population (target population), …, thus minimizing the need to generate additional information (*types of studies, design modifications, n of patients required*) to reach conclusions for the target population,...

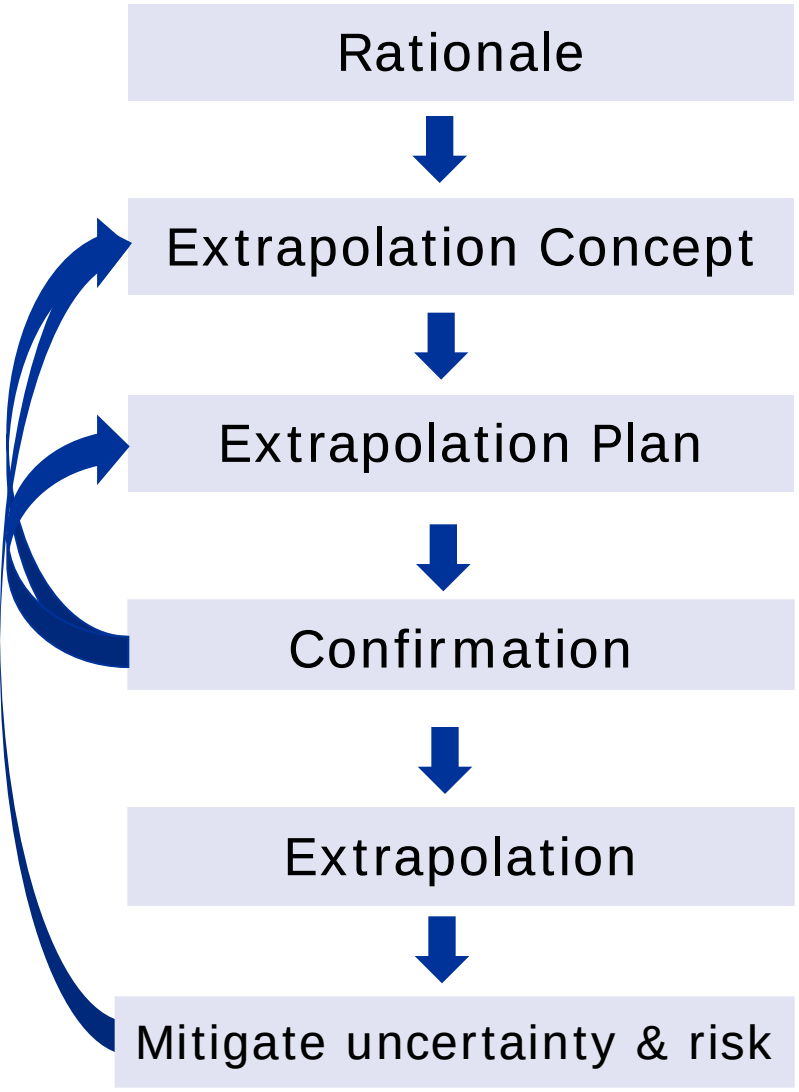
EMA 2016, Reflection paper on extrapolation of efficacy and safety in paediatric medicine development

Rationale for extrapolation

1. **To avoid ‚unnecessary' studies** – if extrapolation from other sources is scientifically justified
   - ethics / ressource allocation / efficiency

2. **Feasibility restrictions**
   - Apply extrapolation principles for rational interpretation of the limited evidence in the context of data available from other sources

Extrapolation Framework



- To perform only necessary studies
- Feasibility restrictions

- Systematic synthesis of existing data to develop quantitative predictions on PK/PD, the disease, and clinical response in the target population

- Studies required in target population to complete the knowledge gaps. Reduced data requirements in accordance with predicted degree of similarities.

- Use emerging data to confirm previous predictions or, if needed adapt EP concept & plan

- Interpretation of the limited data in the target population in the context of information extrapolated from the source population

- Strategies to further confirm conclusions and mitigate risks

SOURCE POULATION Adults

TARGET POPULATION Children, paediatric age groups

Extrapolation concept

	Pharmacology Drug disposition & effect	**Disease manifestation & progression**	**Clinical response to treatment**
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, size, maturation, etc - disease, comorbidity,	Quantitative synthesis of natural disease data Disease progression models Covariates: - age, maturation - 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		
Prediction	Predict dose to achieve - similar exposure, or - similar PD effect, and - acceptable safety per age group	Describe/predict differences in natural course of disease progression by age group	Given similar drug exposure or PD response, predict degree of differences in - efficacy & safety - benefit-risk balance by age group
	➢ refine predictions using emerging data		

Extrapolation plan

Proposed measures and studies in target population

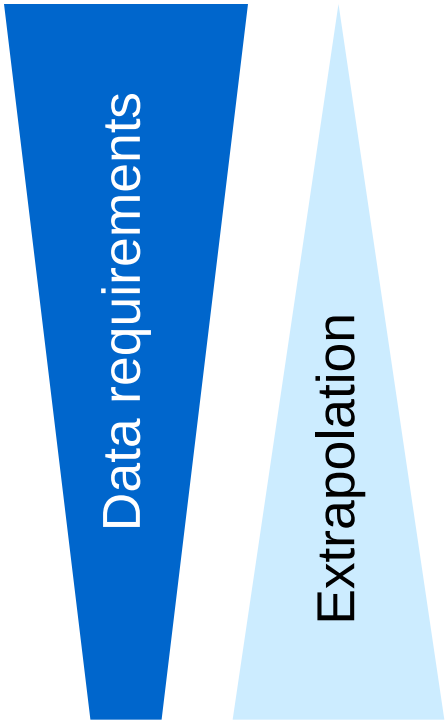
- To complement the information extrapolated from source population(s)
- To confirm the extrapolation concept

	Pharmacology	Disease	Clinical response
Extrapolation plan	PK studies or PK/PD studies needed for confirmation of doses in target population	Epidemiological data - natural history data - SOC treatment in target population	- Design of clinical studies - Sample size(s) in target population to conclude on B/R balance

Extrapolation plan

Reduction of data requirements in accordance with

- predicted degree of similarities
- strength of evidence (degree of uncertainties)



- No extrapolation:
  - Full paediatric study programme
- Extrapolation:
  - Controlled E&S study with reduced sample size
  - Non-controlled ‚descriptive' E&S study
  - Dose-ranging study
  - PK or PK/PD study
  - etc.

Confirmation

Use of emerging data to

- Validate the modelling approaches used for extrapolation
- Confirm the PK / PD model assumptions and predictions
- Confirm the predicted degree of differences in disease progression and clinical response (efficacy, safety)

  - ➢ Alternatively, revisit assumptions and adapt extrapolation concept and plan
  - ➢ Iterative loops of prediction, data generation and confirmation, or adaption, when moving through the phases of development and into successive age subsets

Extrapolation

Interpretation of the data generated in the target population in the context of information extrapolated from the source population (using models updated with the new data)

- Establish appropriate doses, exposures, PD response
- Conclude on efficacy and safety and benefit-risk balance in target population

Mitigating uncertainty and risk

With increasing degree of extrapolation

→ decreasing amount of data for validation

⇒ increasing risk of false conclusions

➢ Collateral criteria and measures:

- Biological plausibility (in-vitro, preclinical and clinical data)
- Iterative loops of model building and data generation
- Concordant responses on different endpoints
- Prospectively planned meta-analysis including future trials
- Further validation by post-authorisation data
- Validation of extrapolation approaches over several developments in related conditions, or related medicines

Many issues to be resolved ...

How to

- weigh the strength of prior information?
- quantify similarity of PK/PD, disease progression, clinical response?
- quantify the uncertainty of extrapolation assumptions?
- integrate expert judgement in the extrapolation concept?
- link degree of similarity with reduction in data requirement
- validate assumptions in the extrapolation concept?
- interprete data in target and source population in conjunction?
- deal with uncertainty and risk?
- analyse and report post-authorisation data to support extrapolation?

How to quantify similarity?

Summary

Key elements of extrapolation framework

- Systematic and quantitative synthesis of existing data, using M&S, on the similarity between source and target population on several levels (PK/PD, disease progression, clinical response)
- Quantitative (rather than qualitative) predictions on the degree of similarity in the target population
- Reduction of the data required in the target population in accordance with the predicted degree of similarity
- Iterative loops of prediction, data generation and confirmation, or adaption of the development plan, using M&S in planning & analysis
- Continuing confirmation/re-evaluation in post-authorisation phase