Orphan Drug Development Guidebook

Building Block I402

This document defines the content of the Building Block created for each identified tool, incentives, initiative or practice introduced by public bodies or used by developers to expedite drug development in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	Extrapolation of efficacy and safety in medicine development (Extrapolation)
References	https://www.ema.europa.eu/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf https://www.ema.europa.eu/en/events/ema-public-workshop-extrapolation-efficacy-safety-medicine-development Extrapolation of Adult Data and Other Data in Pediatric Drug-Development Programs. Pediatrics 2011;128;e1242 https://www.ncbi.nlm.nih.gov/pubmed/22025597 Extrapolation of Efficacy in Pediatric Drug Development and Evidence-based Medicine: Progress and Lessons Learned. Ther Innov Regul Sci 2017; 2017: 1-7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5587157/pdf/nihms901908.pdf General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products: Guidance for Industry https://www.fda.gov/downloads/drugs/guidances/ucm425885.pdf Pediatric Rare Diseases- A Collaborative Approach for Drug Development Using Gaucher Disease as a Model: Guidance for Industry https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM587660.pdf
Description	The EMA describes extrapolation as extending information and conclusions available from studies in one or more subgroups of the patient population (source population(s)), or in related conditions or with related medicinal products, in order to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the amount of, or general need for, additional

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	evidence generation (types of studies, design modifications, number of patients required) needed to reach conclusions. The FDA states that extrapolation of efficacy can be considered when the course of the disease and the expected response to a drug product would be sufficiently similar in the pediatric and reference population (i.e., adult or other pediatric age population). The FDA emphasizes that dosing and safety cannot be extrapolated; effects of therapy on specific pediatric manifestations (i.e. growth rate, onset of puberty and progression of pubertal development) cannot be extrapolated. Costs to develop / plan the framework for extrapolation may exist but in the long-term extrapolation may save money
Category	Development Resource Building Block
Geographical scope	Europe, USA
Availability	In rare disease research, due to the small numbers of subjects, it is particularly important to utilise efficiencies. Therefore, it may be appropriate to use available clinical information in one area to support other aspects of the drug development programme where modelling and simulation can be used, reducing the burden of conducting multiple clinical trials.
Scope of use	Main examples can be found in extrapolating efficacy from adult data to the paediatric population, potentially streamlining the drug development programme. There is also increasing interest in basket studies, where extrapolation between groups may be required. Paediatrics, basket studies, modelling and simulation
Stakeholders	Drug developers, regulatory authorities
Enablers/ Requirements	Scientific advice with the Central and National Regulatory Authorities is strongly recommended regarding the acceptability of extrapolation proposals
Output	Component of the drug development pathway

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Best time to apply and time window	Early in the development plan so that the approach can be factored into the overall approaches to support marketing authorization.
Expert tips	Consider early in the development pathway, consider modelling and simulation (M&S) question and answers or other regulatory support https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers **PROs**: • Can speed up the drug development and reduce the need for clinical trials **CONs**: • Approach should be agreed by seeking scientific advice from regulators