



**E11(R1) Addendum to E11:
Clinical Investigation of Medicinal Products
in the Pediatric Population**
Step 4

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International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use



E11(R1) : Clinical Investigation of Medicinal Products in the
Pediatric Population

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Background to E11(R1)

E11, published in 2000, outlined following points to consider in pediatric drug development:

- Need for appropriate formulation and toxicity consideration of excipients.
- Recommendation of timing and types of studies to facilitate pediatric drug development especially in the context of development for adult indications.
- Classification of pediatric population by age.
- Ethical considerations particular to pediatric population
- Necessity and consideration to develop pediatric drugs for indications in children.

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Scope and Objectives

Scope of E11 and E11(R1) include consideration points for planning and executing pediatric drug development in several specific areas: timing of development, types of studies, age categories, pediatric formulations, and ethical considerations.

E11(R1) supplements E11 in several areas, reflecting various process improvements in pediatric drug development, especially in extrapolation, modelling and simulation (M&S), and trial methodology.

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Table of Contents of E11(R1)

- Ethical Considerations
- Commonality of Scientific Approach for Pediatric Drug Development Programs
- Age Classification and Pediatric Subgroups, including Neonates
- Approaches to Optimize Pediatric Drug Development:
 - The Use of Extrapolation in Pediatric Drug Development
 - The Use of Modelling and Simulation in Pediatric Drug Development
- Practicalities in the Design and Execution of Pediatric Clinical Trials
- Pediatric Formulations

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Ethical Considerations

- Definitions of child assent and informed consent / permission by parents (guardian).
- Emphasis on need to update information given to a child in long term study to accommodate child's understanding.
- Necessity to obtain informed consent when a child reaches adult age of consent.

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Commonality of Scientific Approach for Pediatric Drug Development Programs

- Pediatric drug development is often multiregional.
- Regional differences can limit the ability for regulatory authorities to align requirements. Hence, a need to address these difference through a common scientific approach.
- Lists nine questions to consider in assembling pediatric drug development strategy.
- Early consideration of pediatric development plans in overall development, along with early interactions with regulatory authorities can facilitate agreement on a common scientific approach.

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Age Classification and Pediatric Subgroups, including Neonates

- Selection of a pediatric study population needs scientific consideration.
- Chronological age alone may not be an adequate determinant to define developmental subgroups in pediatric studies.
- Arbitrary division of pediatric subgroups by chronological age without scientific basis could unnecessarily limit study population.
- It may be justifiable to include pediatric subpopulations in adult studies or adult subpopulations in pediatric studies.
- Definition of neonatal period for term and preterm new-born infants are provided for use in drug development.
- Consider that neonatal population represents a broad maturational range and conditions that affect this population can vary substantially.

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Approaches to Optimize Pediatric Drug Development The Use of Extrapolation in Pediatric Drug Development

“Pediatric Extrapolation” defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.

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The Use of Extrapolation in Pediatric Drug Development- 6 points to be discussed

1. Evidence to support common pathophysiology, natural history, and similarity of disease course between reference and pediatric population(s).
2. Strength of evidence of efficacy in reference populations.
3. Availability of biomarker or surrogate endpoints in the reference populations relevant in the pediatric population.
4. Evidence to support exposure-response similarity between reference and intended populations.
5. Uncertainties of existing data and remaining uncertainties about pediatric population.
6. Additional information to be generated (e.g., information from M&S, animal, adult, pediatric subgroup studies) in order to inform the acceptability of the extrapolation approach.

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Approaches to Optimize Pediatric Drug Development

The Use of Modelling and Simulation in Pediatric Drug Development

Advancement in clinical pharmacology and quantitative M&S techniques has enabled progress in utilizing model-informed approaches in drug development. M&S can help quantify available information and assist in defining the design of pediatric clinical studies and/or the dosing strategy.

Considering the limited ability to collect data in the pediatric population, M&S can be a useful tool to address knowledge gaps in pediatric drug development and inform on pharmacokinetics, pharmacodynamics, efficacy and safety of a drug.

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The Use of Modelling and Simulation in Pediatric Drug Development - Approach

- Incorporation of M&S into pediatric drug development should be based on a strategic plan through multidisciplinary discussions.
- Criteria to be considered include intended use of a model itself, quality and extent of existing data, and assumptions made.
- Important to consider maturation of organ systems: data from older subgroups may not necessarily be informative for the younger subgroups.
- Risks of consequences of a specific approach should be discussed with experts.
- Risks associated with accepting the M&S assumptions should be assessed and managed prospectively.

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Practicalities in the Design and Execution of Pediatric Clinical Trials

Aspects of pediatric clinical trial practicality: feasibility, outcome assessment, and long term clinical aspects including safety.

- Try to improve feasibility through clinical trial networks, expanding participating facilities, implementing various operational strategies, collaborating with patient support organizations, among others.
- Consider appropriate endpoints for specific age and developmental subgroups.
- Trial design should allow pediatric participants to contribute directly in outcome measures if appropriate.
- Assess potential pediatric endpoints in adult development program.
- Plan for long term safety data collection, considering effects of drug treatment in child's development, growth, and/or maturation of organ/system function, with early planning for baseline data collection.

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Pediatric Formulations

- Pediatric formulations consideration: age-appropriate dosage forms and acceptability help optimize efficacy and reduce risks of medication and dosing.
- Excipients with less risk to children should always be considered, weighed against the severity of the disease and availability of alternative treatments.
- Developing drugs for neonates require special attention: its physiological effect, method of delivery, and environment of usage.

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Key Principles

- E11 and E11(R1) provide ethical and scientific principles that should be considered in developing safe and effective pediatric medicinal products.
- Specific ethical, scientific and social aspects of children necessitate maximum evidence obtained from smallest possible number of study participants with adequate safeguards.
- Innovative approaches to accomplish such goal should be discussed early with regulators.

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E11(R1) : Clinical Investigation of Medicinal Products in the Pediatric Population

Considerations

- In general, early and continual conversations between stakeholders and regulatory authorities on pediatric drug development will facilitate the entire process.
- Guidance in E11(R1) on pediatric extrapolation and M&S are of high level and therefore technical details should be discussed with regulatory authorities as the knowledge and experience in these fields evolve.

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Implementation

ICH E11 and E11(R1) provide integrated guidance to pediatric drug development in multiregional settings in order to address global need for evidence on use of safe and effective pediatric medicinal products.

Public consultations on *Step 2b* document were conducted in the following regions:

- USA
- Europe and Switzerland
- Japan
- Canada
- Brazil (limited basis)

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Thank You!

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