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- Beyond Innovation -

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ICH E11 and Pediatric Drug Development

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ICH E11

- **ICH E11** final version adopted on July 2000

  Clinical Investigation of Medicinal Products in the Pediatric Population

  Implemented in Japan on December 2000

- **ICH E11 (R1)** final version adopted on August 2017

  Addendum to ICH E11

  Implemented in Japan on December 2017

- **ICH E11A** ongoing (This topic was endorsed by the ICH Assembly in June 2017)

  Pediatric Extrapolation

Historical Background of ICH E11

- The development of medicinal products for pediatric use has not been progressing easily.
  - So-called “Therapeutic Orphans”
- Pediatric dosages are not approved for most medicines.
- Despite not specifying the appropriate effect-efficacy or dosage and administration, many medicines are administered to children.

These situation were similar among in Japan, the US and the EU.

Jpn J Clin Pharmacol Ther. 2002; 33: 515S

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Therapeutic Orphans

A term coined in 1968 by Dr. Shirkey for the lack of studies about the safety, dosing and efficacy for medicines used in children which have been approved for adults.

Shirkey HC, Therapeutic Orphans. *J Pediatr*.
1968; 2: 119-120. Editorial comment

History of ICH E11

Rapporteur: PhRMA

FEB 1998	Washington, D.C. Meeting The EU proposed the building of international guidelines for pediatric clinical trials.
SEP 1998	Tokyo Meeting The concept paper was submitted.
JAN 1999	London Meeting 1st Expert Working Group Meeting was held.
MAR 1999	Brussels Meeting Draft of guidelines was created.
OCT 1999	Washington, D.C. Meeting Step2
NOV 2000	Final draft of the guidelines were signed up.

Jpn J Clin Pharmacol Ther. 2020; 33: 515S

Objectives of ICH E11

- It is the goal of this guidance to encourage and facilitate timely pediatric medicinal product development internationally.

- The guidance provides an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population.

General Principles of ICH E11

- Pediatric patients should be given medicines that have been appropriately evaluated for their use.
- Development of product information in pediatric patients should be timely and often requiring the development of pediatric formulations.
- Drug development programs should include the pediatric studies when pediatric use is anticipated.
- The rights of pediatric participants should be protected and they should be shielded from undue risk.
- This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole.

Scope of ICH E11

E11 outlined the 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.

Laws and Regulations in Pediatric Drug Development in Japan, the US and the EU

United States:	
1977	American Academy of Pediatrics Committee on Drugs – Report on study of drugs in children[64]
1979	Food and Drug Administration (FDA) articulates how to provide information on labelling
1983	45 Code of Federal Regulations (CFR) 46 Subpart D regulations: Additional Protections for Children Involved as Subjects In Research
1997	FDA Modernization Act/Exclusivity Provision[73]
1998	Pediatric Rule Regulation (enjoined 2002)[25]
2000	Guidance for Industry: International Conference on Harmonization (ICH) E11 Clinical Investigation of Medicinal Products in the Pediatric Population[66]
2001	Subpart D regulations adopted by FDA: Additional safeguards for children in clinical investigation of FDA-regulated products[13]
2002	Best Pharmaceuticals for Children Act (BPCA)[27]
2003	Pediatric Research Equity Act (PREA)[28]
2007	BPCA and PREA re-authorized by Congress[29]
Europe:	
2000	Regulation No (EC) 141/2000 on orphan medicinal products[74]
2000	ICH E11 Note for guidance on clinical investigation of medicinal products in the paediatric population[64;65]
2001	Directive 2001/20/EC Good Clinical Practice in Clinical Trials[17]
2003	Commission Directive 2003/94/EC principles and guidelines of good manufacturing practice[75]
2005	Commission Directive 2005/28/EC principles and detailed guidelines for good clinical [76]
2007	Paediatric Regulation No 1901/2006 and 1902/2006[21;30]
Japan:	
2000	Notification No. 1334: Clinical studies on Drugs in Pediatric Populations (ICH E11)[67]

https://www.who.int/childmedicines/publications/GUIDANCECHILDHEALTH.pdf?ua=1

Scope and Objective of ICH E11 (R1)

Rapporteur: PhRMA
Regulatory Chair: PMDA

- Pediatric drug development has evolved since the original ICH E11 Guideline (2000), requiring consideration of regulatory and scientific advances relevant to pediatric populations.

- This addendum does not alter the scope of the original guideline which outlines an approach to the safe, efficient, and ethical study of medicinal products in the pediatric population.

Table of Contents of ICH E11 (R1)

1. Introduction
    1.1. Scope and Objective of the ICH E11 Guideline Addendum (R1)
2. Ethical Considerations
3. Commonality of Scientific Approach for Pediatric Drug Development Programs
4. Age Classification and Pediatric Subgroups, Including Neonates
5. Approaches to Optimize Pediatric Drug Development
    5.1. The Use of Existing Knowledge in Pediatric Drug Development
        5.1.1. The Use of Extrapolation in Pediatric Drug Development
        5.1.2. The Use of Modelling and Simulation in Pediatric Drug Development
6. Practicalities in the Design and Execution of Pediatric Clinical Trials
    6.1. Feasibility
    6.2. Outcome Assessments
    6.3. Long-term Clinical Aspects
7. Pediatric Formulations
    7.1. Dosage and Administration
    7.2. Excipients
    7.3. Palatability and Acceptability
    7.4. Neonates
8. Glossary

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ICH E11A

Pediatric Extrapolation

Definition from E11 (R1)

"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.

6 Points to be Discussed for the Use of Extrapolation in Pediatric Drug Development

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 a biomarker or surrogate endpoint 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.

Background of ICH E11A

Rapporteur: FDA

- ICH E11(R1) concept paper recommends that more detailed guidance be developed to advance the use of pediatric extrapolation.
- ICH E11(R1) guideline only includes a high level description of pediatric extrapolation that encourages sponsors to initiate a discussion of using this approach in regulatory interactions.

Therefore, there is a need to provide more detailed guidance about how pediatric extrapolation can be used in successful pediatric product development, leading to marketing authorization.

Objectives of ICH E11A

- Address and align terminology related to pediatric extrapolation
- Provide information on various approaches that can be utilized to support the use of pediatric extrapolation
- Discuss a systematic approach to use of pediatric extrapolation
- Discuss study designs, statistical analysis, modeling and simulation analyses and respective methods

Complex Guidance requiring participation of experts from multiple disciplines (clinical, clinical pharmacology, pharmacometrics, and statistics)

Three Major Topics discussed in ICH E11A

- Disease Similarity
- Modelling & Simulation
- Statistical methodology

E11A Expert Working Group

<Regulatory Members>

ANVISA, Brazil
EC, EU
FDA, US
Health Canada, Canada
MFDS, Republic of Korea
MHLW/PMDA, Japan
National Center, Kazakhstan*
NMPA, China
TFDA, Chinese Taipei
TGA*
WHO*

<Industry Members>

BIO
EFPIA
Global Self-Care Federation
IFPMA*
JPMA
PhRMA

*: Observer

As of OCT 2020

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Key Milestones

Completion date	Milestone
OCT 2017	Concept paper endorsed by Management Committee
OCT 2017	Business plan endorsed by Management Committee
JUN 2018	Completed review of global literature on pediatric extrapolation
JUN 2018	Completed review of pediatric extrapolation issues from E11(A) public comments
NOV 2018	Completed draft table of contents outline of guidelines
JUN 2019	Completed detailed outline of guidelines
NOV 2019	Began review of first draft of guidelines

Expected completion date	Milestone
DELAYED	Step 1 Consensus building, drafting of Technical Document
DELAYED	Step 2a ICH parties consensus on Technical Document

Take Home Message

- E11 and E11 (R1) provide ethical and scientific principles that should be considered in developing safe and effective pediatric medicinal products.
- E11 has contributed to promote pediatric drug development.
- Cooperation among all stakeholders such as companies, regulatory authorities, health professionals and patients and/or parents is necessary for the success of pediatric drug development. International collaboration is also important.

Thank you for your attention

PMDA strongly supports pediatric drug development.

Better medicine for children!