

**COMPARATIVE ANALYSIS OF GLOBAL PEDIATRIC DRUG DEVELOPMENT
REGULATIONS: EMERGING TRENDS AND FUTURE HARMONIZATION**Chaya M.*¹, Sanjana P. S.², Sai Nikhil V.², Nithya T.², Namratha V.², Yukthashree R. I.²¹Associate Professor, Department of Pharmaceutics.²Sree Siddaganga College of Pharmacy, Tumkur.***Corresponding Author: Chaya M.**

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ABSTRACT

The study and development of paediatric medications focus on ensuring the safety, effectiveness, quality, and appropriate dosages of medications. The materials used to regulate the creation of drugs are crucial, and the methods followed for better harmonisation. The development of paediatric drugs is governed by the US Food and Drug Administration, the European Medicines Agency, and the central drug standard control organisation. These organisations adopt ICH recommendations such as ICH E11/E11(R1) and ICH S11 as part of their framework. Comparative analysis of paediatric drugs at the global level for better drug action depends on metabolic rate and regulatory protocols in both children and adolescents.

KEYWORDS: Pharmaceutical innovation for children; comparative evaluation; paediatric formulation; Paediatric pharmacovigilance.

INTRODUCTION

Medications used to treat illnesses in children are known as "Paediatric medicines".

Comparative analysis of global paediatric drug development regulation, a continuous process in the regulation of paediatric drug development. Its main intention is to target new scientific and regulatory approaches in different Countries for safe and effective medicine for children and adults.^[1]

Medication administration follows a proximal-to-distal and cephalo-caudal pattern that is dependent on functional maturation of the CNS. In July 2000, establishment of paediatric development regulation on Clinical Investigation.^[2]

According to ICH E11 Guideline

Age-appropriate formulation is a guideline for drug absorption, metabolism, dose requirements, and growth and development differences.

Neonate = 0-28 days

Infants = 1month-1year

Child=2-10 years

Adolescent= 11-17years.

Different stages require different dosing of formulations.

Dosage

Every age group has its own unique set of challenges throughout the drug development process. Adult outcome measures may not translate to the paediatric population.

Based on the physical forms of the drugs, the dosage form is classified as:

1. Liquid dosage forms

- Syrups
- Elixirs
- Solutions

2. Solid dosage form

- Tablets
- Chewable

3. Suspension dosage form

- Dispersed in liquid

4. Semi-solid dosage form

- Ointments
- Creams
- Gel

5. Parenteral dosage form

- Injections
- When oral administration is not suitable.^[3]

Paediatric development regulation

In the USFDA (United States Food and Drug Administration), administering drugs on ages of patients span from newborns to younger ones. The classification of patients based on their age group, it includes:

Neonates	Birth -27 days
Infants	28 days- 23 months
Children	2 years- 11 years
Adolescents	12 years- 16 years

[4]

It is strongly regulated by PREA and BPCA. Criteria for patient age categorisation are defined by the European Medicines Agency (EMA), which states that:

a) Neonates

Pre- term	Before birth
Post- term	Birth- 27 days

b) Infants and toddlers: 28 days- 23 months

c) Children: 2 years- 11 years

d) Adolescents: 12- below 18 years^[5]

According to India, CDSCO (Central Drugs Standard Control Organisation) defines classification of patients based on their ages from birth to 18 years.^[6]

History and Evolution of Paediatrics development

In the early 19's and 2000's, a voluntary study in paediatrics. Due to a small market, difficulty in formulation, and were expensive to manufacture, the drug programme was limited in the early period.

Paediatric drug tragedies

1905: Death from patent medicines

1936: Sulfanilamide dissolved in diethylene glycol kills 107 people

1961: Thalidomide causes limb deformations

As a result of this, regulatory acts came into effect and formed the regulations aiming to set an end to or lessen the frequency of such actions.

Those acts include

1906: Pure food and drug act

1937: Federal Food, Drug, and Cosmetic Act

1962 Kefauver-Harris Amendment (Effective for their labelled indication).

A lack of sufficient data on paediatric patients has led to such disasters such as

- Grey baby syndrome from chloramphenicol
- Phocomelia from thalidomide.

In order to regulate paediatric research, the US Food and Drug Administration (FDA) set standards for development.

- RACE for Children Act: The act focuses on specific mechanisms for children about children growth and medical tests for healthy development.
- PREA (Paediatric Research Equity Act) and BPCA (Best Pharmaceuticals for Children Act): United States Food and Drug Administration strongly regulates paediatric development by developing PREA (Paediatric Research Equity Act) and BPCA (Best Pharmaceuticals for Children Act) for paediatric studies.

European Union (EMA) establishes a PIP (Paediatric Investigation Plan) for paediatric Studies. The approach's development is focused on acquiring knowledge about the formulations. Ethical consideration in all frameworks.

In India, CDSCO regulates paediatric clinical research within the regulatory framework, on safety studies in paediatric drug development.

ICH guidelines ICH E11/E11 (R1) and ICH S11 drug involves the major assessment in guidelines for the development of a medication with an existing paediatric indication. Clinical investigation of medical products in Paediatric population was established in July 2000.

Emerging trends in paediatrics

- Paediatric Extrapolation in adult children with appropriate data reduces the need for certain clinical studies.
- Modelling and simulation help to select suitable doses and improve the design of paediatric studies.
- Age-appropriate formulations: Greater focus on medication that is easy and safe for children to take.
- Guidelines such as ICH E11 (R1) and ESSA are helping Countries follow more consistent approaches.^[7]

Further Harmonization

- On harmonisation, Every Country has their own approaches for the growth of medication.
- As part of the ICH E11/E11(R1) and ICH S11, certain guidelines are followed for consistent growth of medication.
- In the USFDA, European Union, India (CDSCO) and certain international regulatory guidelines, are the main source for the development of paediatric drugs. These guidelines cover aspects such as clinical trials, age-appropriate classification, safety, and effective standard treatment. The medical community involves specific work in advancing the therapeutic process and model-informed drug development.

- Harmonizing the similar guideline for paediatrics throughout the world has to be implemented in order to increase the severity in implementation of critical guidelines at all the stages of the manufacturing process in order to maintain quality, safety and efficacy of the drugs.
- Implementation of AI-ML technology for early detection of patient health and treating them with the adoption of suitable medical devices for children.^[3]

MATERIALS AND METHODS

Paediatric drug development is an important area in terms of growth, body size, organ function development, metabolism and physical strength that differ easily. There are some important factors, like diversity of children across different age groups, procedures to obtain consent, recruiting participants and various ethical considerations.

Regulatory guidelines and ethical considerations.

FDA and EMA involve certain specific guidelines for the pharmaceutical industry to follow, including required procedures, scientific and other guidelines that influence paediatric drug development.

Ethical Consideration performs serving a crucial function in paediatric clinical studies; as children are a vulnerable population, the main goal is to protect the safety of children.^[6]

FDA paediatric guideline

Qualifying for paediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act: PREA and BPCA for development regulation.

- ICH E11 – Clinical investigation of medicinal products in the paediatric population
- ICH E11(R1) – Addendum to ICH E11, it covers clinical trial design, drug formulation and modelling
- ICH E11A – Paediatric extrapolation
- Paediatric Research Equity Act (PREA) in 2003 – mainly works on safety and effectiveness in relevant paediatric age groups.
- Best Pharmaceuticals for Children Act (BPCA) 2002 – Encourage pharmaceutical companies to conduct paediatric studies.^[9]

EMA Paediatric guideline

Guideline on the investigation of medical products in term and preterm neonates.

Ethical considerations for clinical trials according to EMA guidelines that involve medicinal products in paediatric population. The volume of blood collected should be kept to a minimum and justified in the study protocol.

- EU Paediatric regulation (EC) No.1901/2006 – organised in 2007 to promote development of medicines for children in high quality and ethical clinical research.

- Paediatric Investigation Plan (PIP) – helps to ensure that paediatric research is planned early in drug development.
- Paediatric Committee (PDCO) – Assesses paediatric Investigation Plans
- Paediatric Use Marketing Authorisation (PUMA) – Encourage research medicines for paediatric use.^[10]

Methods

Clinical trials are effective in identifying physiological and developmental differences between children and adults for safety, efficacy, pharmacokinetics and pharmacodynamic action process on body.

Models, simulations, and paediatric Extrapolation in adults or childhood-appropriate data reduce the need for certain clinical studies and improve the design of Paediatric studies.

Under ICH guidelines, ICH E11/E11 (R1) and KH S11 involve or release certain guidelines for consistent growth of medication.

All information from the USFDA, European Union, and Indian (CDSCO) were analysed and developed for further global paediatric development harmonisation. Paediatric involves development in pharmacovigilance, physiological development, pharmacokinetics, pharmacodynamic, paediatric formulation, dose selection are major components of paediatric drug development aspects for infants, children and adult.

List of uses in paediatric development for infants, children and adult through better implementation of paediatric guidelines. The advantages include:

- Tracking age-appropriate formulation
- Advanced Extrapolation methods
- Redundant Clinical trial elimination
- Disease management.

Disadvantages if paediatric drugs are not implemented for children and adult at specific dosage and time interval between the doses, it may lead to

- Harmful Exposure to children.
- Severe Adverse drug reactions.
- Impacts on growth and development.^[4-6]

RESULTS AND DISCUSSION

Paediatric drug development regulation mainly follows the US FDA and EMA frameworks for global paediatric development through following ICH guidelines like ICH E11/E11 (R1) and KH S11. Drug development involves major assessment in the development of a paediatric indication.

Drug development is Complex; each age group has its own complexities. Adult outcome measures may not translate in the paediatric population; it requires a team approach & institutional support to succeed.

Paediatric outcome measures in children through implementation of ICH Guidelines for better metabolism and children better health condition in sense of present and further growth and development.

Short term= disease resolution/ improvement (feels / functions/survives)

Long term = growth and development.

In the outcomes measured accepted by the medical Community like group of medical researchers, clinical researcher, paediatricians and regulatory experts for efficacy treatment, diagnosis illness, determine appropriate doses, safety and clinical outcome assessments.

Example= Oral paediatric formulations involve Swallowable

- Palatable
- Dosing accuracy for young children.

Children may have difficulty in swallowing tablets, so researchers like medical researcher, clinical researcher, pharmacologists, ethic committees are actively involved in developing advanced therapeutic processes for further harmonisation in order to maintain better health condition of children.

- Oral liquids

- Dispersible tablets
- Orodispersible formulation

Paediatric drug therapy challenges a doctor / pharmacist since children are different from adults. Some of the assumptions made in adult drug therapy do not apply in children. Only a few drugs approved by the regulatory authorities have indication specific for use in the paediatric population most of medicines have irrelevant action between children and adult drugs, which doesn't have specific age formulation for action drugs having an effective remark on administration of irrelevant drug in children.^[11,12]

Drugs avoided in neonates & infants

Drugs	Remarks
Anabolic hormones	Contraindicated, stunted growth
Aspirin	Reye's syndrome
Chloramphenicol	Gray baby syndrome ^[13]

Unique paediatric risks, vulnerabilities and clinical impact on irrelevant drug administration, age-appropriate dosage, dosage errors, organ immaturity, long term effects, limited clinical data and formulation risks effects the children and adult growth and development in paediatric development.

Vulnerability factor	Biological causes	Clinical impact
Paradoxical reactions	Developing central nervous system indifferent stimuli	Extreme excitability or insomnia on certain antihistamine
Growth consideration	Skeletal system is actively growing	Corticosteroids ^[14] are highly monitored in growth velocity

CONCLUSION

Comparative analysis of Paediatric Development regulation Emerging trends and further harmonization. describe under the guidelines of ICH E11 / E11(R1) followed by US FDA, Europe union and Indian CDSCO regulates different frame work for paediatric drug development on global, which works on development of drugs for neonates, infants, children and Adolescent purpose of safety, efficacy, pharmacokinetic action and metabolism. The regulatory requirement works together for better paediatric drug development.

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