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Review Article

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Comprehensive review and enhancing approaches for Pediatric investigation plan in USA, EU and India

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Abstract

Several various regulations connected to paediatric clinical investigations characterise the regulatory framework in the United States, EU and INDIA. Regulations that govern the requirements for conducting paediatric studies or provide incentives for sponsors to perform such studies have been implemented in these countries. The Food and Drug Administration in the United States has a comprehensive set of paediatric rules. It has established a distinct department for paediatric medication regulations, known as the Pediatric Therapeutics Offices. The FDA Modernization Statute was passed in the United States of America as the first act for paediatric population clinical trials (1997). These laws govern the incentives for drug developers to do paediatric research (after receiving a written request from the FDA) as well as the standards for conducting paediatric clinical trials. In Europe, the 'Pediatric Regulation (EC) No 1901/2006' was adopted in January 2007 to improve the protection of children in research, while India has no special standards for pediatric investigation. In order to promote better medicines for children, regulatory bodies in the United States and Europe have done a terrific job. There is presently no specific rule for paediatric clinical trials in India, however some provisions are included in Schedule Y. For the safety of children, the Indian health authorities must enact separate legislation for clinical trials. Enhancing approaches are needed for all conceivable indications will be assessed based on the product's mechanism of action, data from other development programmes, proof of concept studies, and so on. Pediatric experts will be consulted to examine each indication.

Keywords: Paediatric Regulation, Paediatric investigative plan, US FDA, EMA, AYUSH, Paediatric Committee (PDCO)

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1. Introduction

Pediatric Regulation

The USFDA is proactively introducing Pediatrics Exclusivity (PE). It grants the company or manufacturer exclusive rights to market medications for a period of six months if the company participated in the Pediatrics clinical trial. Pediatrics rules were adopted in 1999, requiring manufacturers to provide required safety and effectiveness data for relevant Pediatrics age groups prior to approval. The paediatric assessment, as defined by Pediatric Research Equity Act (PREA), includes information acquired from paediatric studies using appropriate formulations for each age group for which the evaluation is necessary. According to these laws, any manufacturer must examine the safety and effectiveness of paediatric formulations under specific conditions, and paediatric studies must be conducted in the same way that adult studies are conducted before being used in children. The **Best Pharmaceutical for Children Act (BPCA)** was enacted on **January 4, 2002**, and the PE sections of the FDAMA quickly repealed. The United States published the final guidelines for **21CFR 50 subpart-D on February 29, 2013,** which describe additional protections for paediatricians in clinical study plans for FDA-regulated products. According to USFDA clinical trials in the paediatric population, the **FDA Modernization Act of 1997** gave incentives to undertake clinical trials in paediatrics by providing exclusivity or patent protection. If off-patent medications are not included, but the manufacturer refuses to accept additional paediatric studies, time and provisions have been made mandatory. In August 2020, the FDA will be able to require paediatric studies for any new drugs or biologics whose molecular target is related to the growth or progression of a paediatric cancer under the Research to Accelerate Cures and Equity (RACE) for Children Act, which allows the FDA to require paediatric studies

for any new drugs or biologics whose molecular target is related to the growth or progression of a paediatric cancer.(1,2)

Figure 1. USA Pediatric Regulation

In EU having Various EU rules regarding clinical trials involving human participants, include EU Directive 2001/20/EC on pharmaceutical items. This regulation, in particular Article 4 for the investigation of paediatric clinical trials, does not meet all of the requirements for the protection of children, hence it is deemed insufficient for paediatric protection. The European Pediatrics Regulation number 1901/2006, which supports clinical trial research in the paediatric population, went into effect in January 2007. ICH Guidelines 11- these guidelines govern how studies in the paediatric population are conducted in Europe. (3, 4)

In India, unlike the USFDA and the EMA, there are no special requirements for paediatric clinical studies or paediatric regulation. Instead, clinical studies are based on safety data released in other developing nations or adult doses. Importing and selling drugs that fall under the AYUSH guidelines (Ayurveda, Siddha, and Unani systems) is regulated by the Drug and Cosmetic Act (D&C Act) of 1940 and its rules of 1945. The rules regulate requirements and policies related to manufacturing and clinical trials for newer imported drugs in India that are listed in Schedule-Y. All of the latest imported clinical study-related requirements and procedures are listed in Schedule –Y and regulations 122 A through E. These standards were produced by the Central Drug Standard Control Organization (CDSCO) and meet the requirements of the Declaration of Helsinki, as well as the Indian Council of Medical Research's ethical guidelines for biomedical research on human subjects (ICMR). Informed consent, protocol preparation, such as protocol information – study content and structure, documentation, ethical composition and functions of ethics committee, and special consideration for paediatric patient study information as a vulnerable population are all requirements listed in schedule Y.(5)

2. Pediatric investigation plan

A paediatric investigative plan (PIP) is a development strategy aimed at ensuring that the relevant data is acquired through kid studies to support the approval of a drug for children. A Pediatric Plan is a statement of intent that specifies the paediatric research that the applicant intends to conduct (e.g., pharmacokinetics/ pharmacodynamics, safety, and efficacy).

I. USA: PIP stands for Pediatric Study Plan, and it is an outline of the paediatric study that the sponsor intends to conduct, including objectives and design, age groups, relevant endpoints, and statistical approach, as well as any planned request for a deferral, partial waiver, or waiver, if applicable, and any supporting documentation or other information FDA requires. (6)

II. EU: European PIP Basis for development and authorization of a pharmaceutical product for all paediatric demographic subgroups, including details of the timeline and suggested measures to show Quality, Safety, and Efficacy to be agreed upon and revised by the PDCO. (7,8)

III. INDIA: According to INDIA, there is no exact definition.

USA: According to the **United States,** a paediatric investigation plan is known as a Pediatric Study Plan, which encourages sponsors to identify paediatric studies as early as possible in product development and, when appropriate, to conduct paediatric studies prior to the submission of an NDA or BLA. FDA encourages (but cannot compel) the inclusion of all paediatric plans, including those that may be studied under the BPCA (i.e., under Written Request), but (e.g., endpoints, efficacy, safety) (9)

- **Initiate Pediatric Studies** :Applicants may begin paediatric trials of medicines and biologics for life-threatening disorders for which there is no effective treatment earlier in the development process than for less serious conditions. (9)
- **As part of the paediatric assessment, data is submitted:** The nature of the application, what is known about the product in paediatric populations, and the underlying disease or condition being treated will all influence the data given under PREA. PREA does not require applicants to do separate paediatric patient safety and effectiveness studies in every situation. (9)

- **FDA Information Must Be Provided :**The rules regulating INDs apply to paediatric trials of pharmaceuticals undertaken under an investigational new drug application (IND), including the content and format requirements of 21 CFR 312.23, as well as the IND safety and yearly reporting requirements of 21 CFR 312.32 and 312.33, respectively.(9)

- **Make a study plan for children:** Since the early 1900s, laws governing the safety and efficacy of pharmaceuticals and biologics have been in place; yet, the inclusion of paediatric usage in drug labelling has lagged greatly. (9)

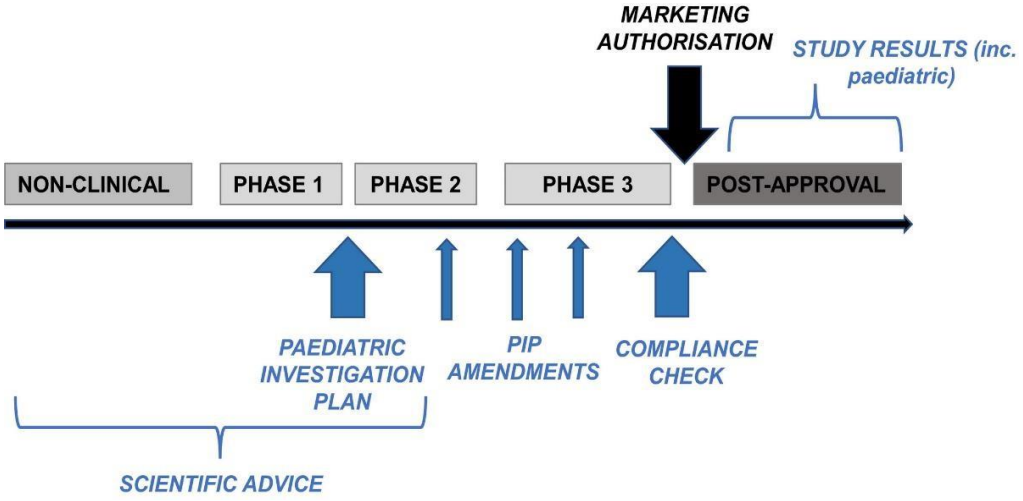

Figure 2. Pediatric investigation plan

- **Initial Pediatric Study Plan Preparation**: All Sponsors who want to submit a marketing application (NDA or BLA) for a medication that includes a new ingredient must submit an iPSP.
    - Ingredient that is active
    - Indication
    - Dosage frequency
    - Dosing schedule
    - Administration route

3. Registration and approval process of PSP

According to the USFDA, a PSP and identification research about paediatric drugs was prepared by the sponsor. PSP must be submitted within 60 days of phase 2 clinical trial completion to NDA or BLA PSP must be submitted no later than 210 days prior to application submission. Registration and approval process of PSP in USFDA which is shown in figure (9)

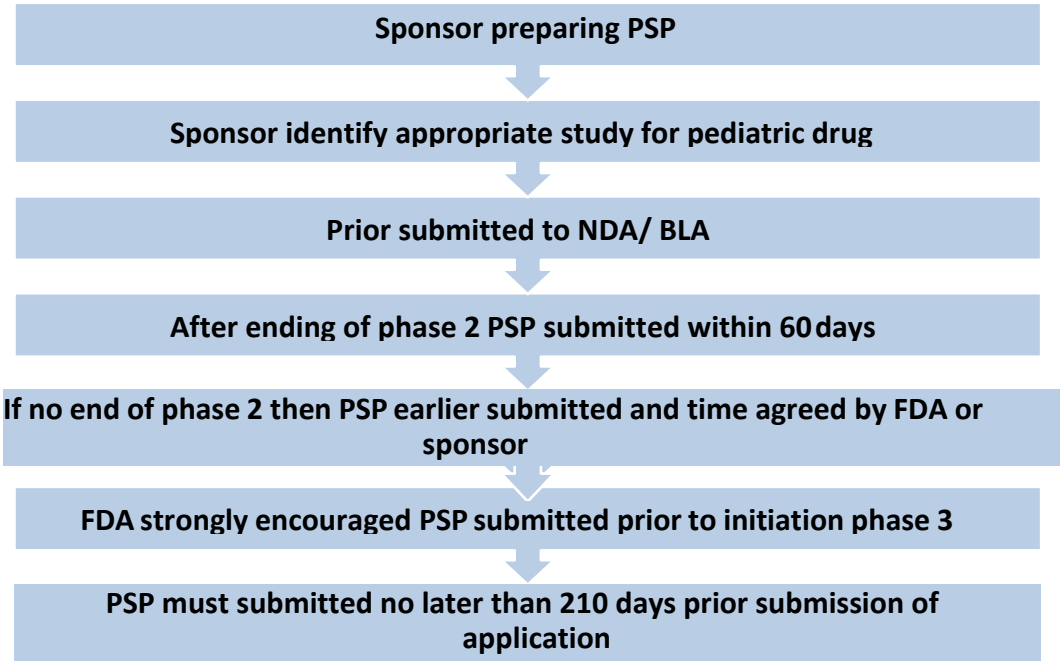

Figure 3. Flowchart of PSP approval process

EU: EMA claims that The Paediatric Committee of the Agency must approve a development plan to support the use of the medicine in children, known as a paediatric investigation plan (PIP). A paediatric investigation plan (PIP) is a development strategy aimed at ensuring that the necessary data for the approval of a drug for children is gathered through research in children. Scientific recommendations developed by the European Medications Agency that are specifically relevant to the development of medicines for children. These guidelines assist applicants in developing paediatric investigation plans and other development programmes for children in order to support child authorization. They are developed in partnership with a number of EMA Committees and Working Parties, including the Paediatric Committee (PDCO) and the Committee for Medicinal Products for Human Use (CHMP) (10)

Pediatric Committee (PDCO): These committees are in charge of promoting the development of newer paediatric medicines in the European Union, as well as other paediatric medicine-related activities that address children's specific needs. The major purpose of these committees is to enhance child health by promoting and discovering medical products at the EU level and enhancing the quality of research. (10)

Pediatric Use Marketing Authorizations (PUMAs): PUMAs are a novel marketing authorisation approach that is issued through a variety of marketing procedures that are specifically applicable to the development of paediatric pharmaceuticals. EMA gets updated clinical research data in paediatric clinical study data, as well as any paediatric studies completed in other countries that are published in the literature, according to PUMA. (11)

Informed Consent: According to item 4(d) of Directive 2001/20/EC, researchers should not put pressure on parent representatives during informed consent. In all circumstances, a parent or authorised representative has the right to know about their child's participation in a trial research without explanation. (2)

Assent from Pediatrics: Child sign-in assent increases with age in order to offer individual information for each age group of clinical study subjects. According to the USFDA, the seven-year period is acceptable, whereas the nine-year period is acceptable in Europe, despite the lack of specific guidelines. (2)

4. Procedure for Pediatric Investigation Plan Registration and Approval in the EU

The flowchart of the PIP approval process is shown in Figure 1. PIP is presented to the PDCO, which investigates deferrals and exemptions and validates them for 30 days before issuing a report to the PDCO, which is then approved. The PIP must be approved by the PDCO, and it can be changed if new information becomes available during the drug development process. Based on ICH guideline 11 and FDA, divides children into age categories. (12)

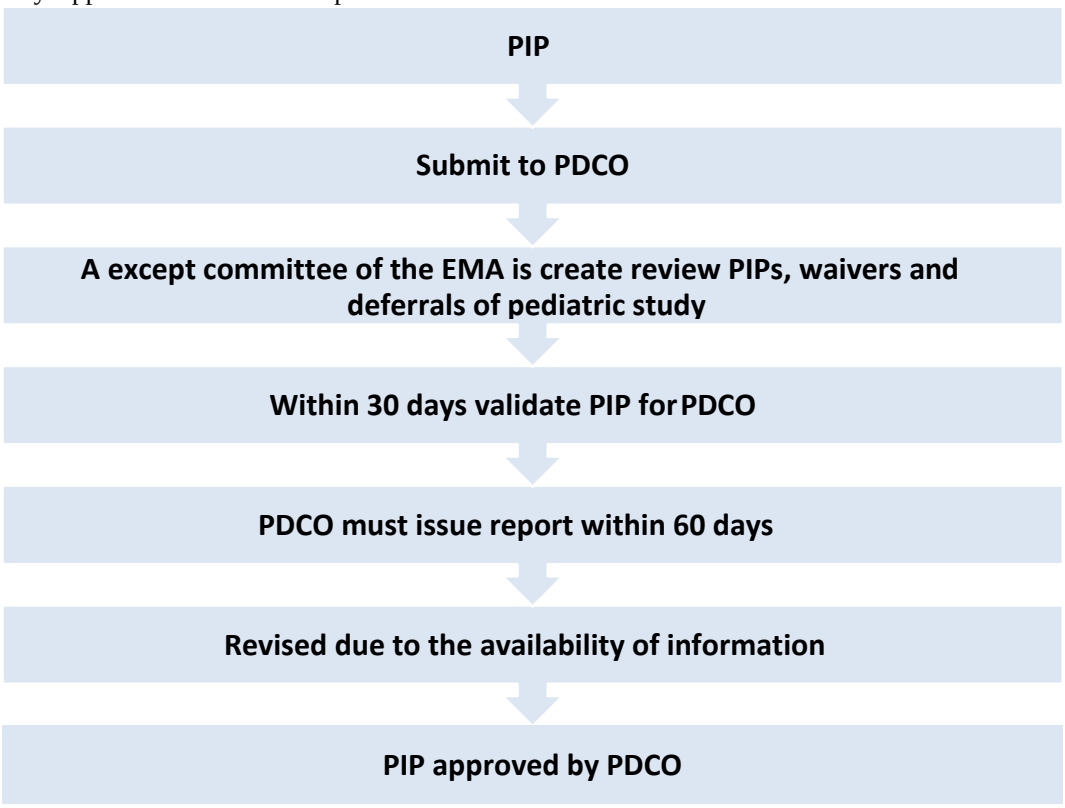

Figure 4. Approval process of PIP in EU

INDIA: Clinical trials in the paediatric population are not subject to any additional regulations. There are no precise guidelines for administering the dose regimen for paediatrics even in routine practise.

Issues for the paediatric population is an especially sensitive population, with major developmental, physiological, and psychological profiles that differ significantly from the adults. During the medication research and development process, these developmental

distinctions must be addressed and taken into account. There is a strong need to include a paediatric drug development regulation as part of the ongoing organisation and restructuring of regulatory guidelines by the Central Drugs Standard Control Organization (CDSCO) to harmonise with global compliances, which will yield more effective results without compromising the safety of the population under discussion. (13)

Ethical considerations and clinical trial design: A list of formulations specifically for paediatric usage should be made available to all. A paediatric-specific clinical trial procedure should be developed to avoid using children as guinea pigs in clinics.

Efficacy and safety compliance: Various research and data acquired from clinical trials should be used to ensure the safety and efficacy of medications for paediatric use in the Indian market. A paediatric subcommittee should advise the regulatory body on the efficacy and safety of pharmaceutical goods (both new and old) in children. Pharmacovigilance in paediatrics should be improved by raising awareness among healthcare providers.

5. Current situation in Indian pediatric investigation Regulation

Clinical trials and methods for a healthy adult human are used to develop paediatric medications in India. There are no special paediatric drug development regulations. Safety and efficacy data from other developed countries, as well as inferences from adult doses, are heavily used in Indian clinical practice. Due to a lack of paediatric-specific guidelines, healthcare providers and caregivers have been forced to estimate doses (either for therapeutic use or for clinical trials) by breaking tablets into quarters and halves, crushing tablets, opening capsules, or proportionally reducing volume if the dose is liquid. It's difficult to administer drugs this way, and it can lead to improper dose, which can lead to decreased efficacy (due to underdoing) and/or safety concerns (due to over-dosing). Children are not to be confused with small adults. (14)

6. Comparative overview of PIP in US, EU and INDIA (2)

The regulatory authorities in the U.S. and the Europe have done good work in this direction to promote better medicines for children.

Table 1. Comparison of Pediatric Drug Development US, EU and India

Item	USA	EU	INDIA
Protocol assistance	All scientific advice provided by FDA	Free scientific advice available for pediatric studies	NO
Criteria for waiver	1) Pediatric studies impossible or highly impractical 2) Ineffective or unsafe	1) Ineffective 2) unsafe in part of pediatric population	NO
Market exclusivity for on- patent drugs	Provides **6 months** of additional marketing exclusivity	Provides **6 months** of additional marketing exclusivity for products and **2 years** of additional marketing exclusivity provided for orphan products	**(7-8 Years)**Time remaining after drug approval from patent life
Market exclusivity for off- patent drugs	**No exclusivity**	**10 years exclusivity** is available for off patent drugs	NO exclusivity

PIP Enhancing approaches

- Determine whether data would be required to begin paediatric research, taking into account the sort of information to be collected in paediatric clinical trials, whether efficacy can be extrapolated, PK and safety may be sufficient, and whether current safety data can be utilised to support safety.
- A paediatric trial's possible sample size must be estimated in order to establish the type of trial design that can be used (e.g., small sample size may be overcome with large treatment effects or longer study period).(15)

The EU and the US take a similar approach

The Pediatric Regulation of the European Union and the US Food and Drug Administration has strengthened the development of medications for children through its system of requirements and rewards. However, there are still opportunities to improve paediatric medical innovations, particularly in terms of regulatory framework implementation.

Within the current legislative framework, considerations include an integrated scientific discussion, the optimization of PIP procedures and compliance checks, and the alignment of study-reporting obligations.

According to the EU

In 2007, the Pediatric Regulation (EC No. 1901/2006) went into effect, creating a working regulatory environment with the goal of increasing high-quality, safe, and ethical research and information on paediatric medicines, as well as facilitating the availability of authorised medicines without the need for unnecessary studies on children or delaying adult approval.

It established the Pediatric Committee (PDCO) inside the European Union and adopted paediatric investigative plans (PIPs).

The European Medicines Agency (EMA) is in charge of evaluating PIPs and sponsors' compliance as well as providing advice on children's medicines.

According to the US Food and Drug Administration (USFDA)

A three-level strategy is used to prioritise needs:

Level 1: Defining therapeutic and therapeutic needs boundaries

Level 2: Needs analysis:

a) Using epidemiology research and literature summaries to identify gaps in treatment areas and/or pharmaceuticals

b) Consultation with paediatric research specialists to identify gaps in therapeutic areas and/or medications (global outreach and Therapeutic Area Expert Panels (BPCA-related working groups)

c) Through FDA consultation, determining labeling /study design gaps

Level 3: Prioritization

Priority Interventions within Therapeutic Areas (priority categories: Affected Patient Population, Unmet Needs, and Scientific Importance) b) Planning Interventions within Therapeutic Areas (evidence, impact, and feasibility Scores) (16)

7. Conclusion

The paediatric population needs extra consideration while prescribing medications because of their immature physiologic systems, as a result, particular rules and regulations for paediatric research are required. According to the United States and the European Union, good approaches and scientific guidelines for paediatric drug development or paediatric investigation plans are available, but India lacks harmonised regulation, that's why India requires urgent attention. According to India, essential medicines are frequently not suitable for use in children. On the other hand, irrational use of available drugs as well as the lack of paediatric specific guidelines for drug development in India, have resulted in adverse drug reactions and drug resistance. (17, 18) The 'Indian Academy of Paediatrics' was founded in Mumbai in 1963 under the Public Trust Act and presently serves as a professional association for paediatricians in India. The Indian Academy of Paediatrics has a membership of 20300 people at the time. The Mumbai Indian Academy of Pediatrics is the organization's headquarters. The Indian Academy of Pediatrics is committed to improving children's health and safety. These academies focus on strengthening Indian paediatric regulation and enhancing paediatric research in India in the future.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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