World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 7.409

"COMPARATIVE ANALYSIS AND ENHANCEMENT STRATEGIES FOR PEDIATRIC INVESTIGATION PLANS IN THE USA, EU, AND INDIA: ADDRESSING REGULATORY FRAMEWORK CHALLENGES AND RECOMMENDATIONS"

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Article Received on 24/10/2024 **Article Revised on 13/11/2024** **Article Accepted on 03/12/2024**

ABSTRACT
The physiological differences between children and adults present special problems for pediatric medication development, requiring customized methods for formulation and dosage optimization. The goal of recent regulatory actions in the US and Europe is to encourage pharmaceutical companies to fund pediatric research. since it leads to significant advancements in the creation of medications for use in children. This study sheds light on the disparities and shortcomings in the treatment of pediatric medical requirements by offering a thorough comparative examination of pediatric drug legislation in the USA, EU, and India. The European Pediatric Regulation (EC) No 1901/2006 places a strong emphasis on enhancing children's protection in research settings, even if the FDA in the United States has set up strong pediatric regulations and incentives to support pediatric research. India is contrasted with these developed nations as a developing nation.

KEYWORDS: Pediatric investigation plan, BPCA, PREA, FDAMA, PDCO, iPSP.

INTRODUCTION
Since the pediatric population is thought to be more sensitive than the adult population, pediatric medication clinical studies must be organized and conducted with specific regard for the ethical and practical aspects of the study.[1] This is because treating children as "small scale and tiny men and women" is inappropriate because the pediatric population represents a variety of distinct physiologies.[2] Children require particular medications and methods for drug development. Compared to adults, their pharmacokinetic and pharmacodynamic reactions are different.

It is imperative to investigate the pharmacological profiles of children across various age groups, as several adult-only medications may have deleterious effects on younger patients. Many medications were provided to children "off label" back then, and regrettably still are, even in the absence of a license or marketing authorization. Every pediatric subpopulation should undergo testing for important medications.[3,4] Clinical trials across a range of pediatric age groups become necessary in order to establish an appropriate dose form for the medications that can be utilized without endangering children.[5] The ethical inclusion of children in clinical studies is widely acknowledged.[6]

Important new information regarding the safety and effectiveness of medications used by children has been produced by the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe since their founding.[7,8] Pediatric medications were developed in India in the past using protocols and clinical trials for healthy adults.[9] Pediatric medication development guidelines or restrictions did not exist. Indian clinical practice mostly depended on adult dose conclusions, as well as safety and efficacy data from other industrialized nations.[10,11]

Due to a lack of pediatric specific recommendations, parents and healthcare professionals had to estimate the dosage by crushing, halving, or opening capsules, or

partially reducing the volume of liquid tablets.[12,13,14] Children in India are increasingly using medications irrationally as a result of the regulatory body of CDSCO not having established any specific rules for pediatric drug development.[15]

Pediatric Regulation

USA: Children under the age of 17 are considered pediatric patients for the purposes of drug regulation. An illustration of a pediatric cohort

- Infants: from birth to less than two years old
- Children: from two to less than twelve years old
- Adolescents: from twelve to less than seventeen years old.[16]

In a proactive manner, the USFDA is implementing Pediatric Exclusivity (PE). If the company took part in the Paediatrics clinical trial, it gives the manufacturer or corporation the sole right to market drugs for a period of six months. Following the adoption of pediatric regulations in 1999, manufacturers were required to provide necessary safety and effectiveness data for pertinent pediatric age groups before receiving approval.[17]

Table 1: USA Legislation and regulations with important pediatric drug regulation impact.[18]

LEGISLATION	IMPACT	YEAR
FDA Modernization act	The FDA may request pediatric trials. Furthermore, if trials are conducted in pediatrics, the sponsors are awarded six marketing exclusivities.	1997
The Pediatric Rule	Required pediatric trails	1998
Children's Health Act	safeguards in place for kids taking part in the study trials	2000
Pediatric Research Equity Act	Needs pediatric Assessment	2003
Food and Drug Administration Amendments Act	Reauthorized BPCA and PREA	2007
Food and Drug Administration Safety and Innovation Act	PREA and BPCA were made permanent. Neonatology knowledge needed in the office	2012
FDA Reauthorization act	Demands that cancer products be evaluated using molecular targets.	2017
Research to Accelerate Cures and Equity for Children Act(RACE)	PREA has been updated, allowing the FDA to mandate pediatric evaluations for cancer medications in cases when the molecular targets have a significant bearing on childhood cancers.	2017

FDA Modernization act: The FDA Modernization Act (FDAMA) of 1997, along with its financial incentives for the pharmaceutical industry to conduct drug trials involving children, has had a detrimental impact on the dignity, health, and well-being of children. These attractive incentives provided a chance to expedite the process of FDA approval for the marketing of pediatric drugs. The implementation of FDAMA marked a significant shift in federal policy to facilitate an increase in pediatric clinical trials. Children, who are unable to provide informed consent for research like adults, are increasingly being targeted as participants in trials even when there is no direct benefit to them. Federal restrictions that forbade children from participating in trials that did not serve their best interests protected them before FDAMA was passed. FDAMA broadened the utilization of 'accelerated approval' pathways for drugs aimed at treating life-threatening conditions, utilizing surrogate endpoints in clinical trials. Furthermore, FDAMA extended the period of market exclusivity for a manufacturer by six months for any patented drug or one in the development phase.[19]

Pediatric Research Equity Act (PREA): Pharma companies must assess the efficacy and safety of novel medications and biologics in pediatric patients (Paediatric Evaluation). Studies are required for both pharmaceuticals and biologicals under PREA.[20] Orphan indications are exempt from PREA study requirements, although pediatric trials need to be identified. By submitting an application for a new active component, dosage schedule, dosing form, mode of administration, or indication, PREA is activated.[21] The creation of a PSP (Paediatric Study Plan) is required prior to submitting an application in PREA. The paediatric research or studies that the sponsor plans to perform are outlined in the paediatric study plan. The PSP aims to encourage sponsors to identify pediatric research opportunities as early in the product development process as possible and, if appropriate, to move forward with those studies prior to filing the NDA or BLA. The FDA strongly advises submitting PSP before to starting Phase 3 research. PSP must be submitted no later than 210 days before the application is submitted.[22]

Best Pharmaceuticals for Children Act (BPCA): The goal of BPCA is to enhance children's drug use and dose safety and effectiveness. In 2002, BPCA was enacted. The U.S. Food and Drug Administration (FDA) Amendments Act of 2007, the FDA Safety and Innovation Act of 2012, and the FDA Reauthorization Act of 2017 all served to reauthorize it. The BPCA laws were most recently renewed in 2022.[23]

The main objectives of BPCA are to

- Provide an extra six months of patent exclusivity to the pharmaceutical sector, which will incentivize them to conduct pediatric research to enhance the labelling of patented drug products used in children.
- Give the NIH permission to use Section 409I to prioritize requirements in a range of therapeutic areas, support clinical trials for off-patent medications that require more research in children, and conduct training programs and other studies to fill in knowledge gaps in pediatric therapeutics.[23]

EUROPE: (Regulation EC No 1901/2006 of the European Parliament and of the Council, amending Regulation EEC No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation EC No 726/2004)) The "Paediatric Regulation" came into effect on January 26, 2007. In order to guarantee that medications used to treat children are the subject of high-quality research and are duly authorized for use in children, the Regulation seeks to "facilitate the development and accessibility of medicinal products for use in the paediatric population.[24] The Regulation of Pediatric Medicines in Europe was Modified Fairly by the Law. The main factor was the establishment of the Paediatric Committee (PDCO), which unifies the Agency's efforts with pediatric medications. The primary duty of the Committee is to oversee and control the research that the pharmaceutical industry is required to carry out on children as part of pediatric investigative plans (PIPs).[25]

The European Commission published a ten-year report on the application of the Paediatric Regulation in October 2017. The study shows that over the last 10 years, children's access to medications has increased across a wide range of treatment categories, most notably rheumatology and infectious disorders. However, it also showed that, particularly with rare diseases, not much progress has been made in treating conditions that exclusively affect children or that show biological distinctions between children and adults. The Commission, EMA, and its PDCO have developed an action plan to enhance the Regulation's implementation in order to address this.[26]

INDIA: Now that we've talked about two developed countries, let's compare the pediatric drug regulatory guidelines of emerging countries like India to those of developed countries like the US and EU. With the exception of minor modifications made to Schedule Y of the Drugs and Cosmetic Act and Rule, we regrettably do not have any specific laws pertaining to medications for children. India has long been a preferred location for clinical trials because of its many advantages, including a sizable patient base, affordable expenses, and ethical freedom.[27]

Many have taken advantage of and exploited the benefits of ethical flexibility in order to perform clinical studies and eventually launch their products. Conducting clinical studies on the pediatric population is not subject to any particular regulations. There are no particular criteria for prescribing the dosage schedule for pediatric patients, even in ordinary practice. Unwanted drug responses have arisen from the illogical use of pharmaceuticals due to the lack of rules tailored specifically for children. A paediatric drug development regulation is desperately needed as part of the ongoing organization and revision of regulatory guidelines by the Central Drugs Standard Control Organization (CDSCO) to harmonise with global compliances. This will produce more effective results without jeopardising the safety of the population under discussion.[27]

Pediatric investigation plan: A development method called a paediatric investigative plan (PIP) makes sure that the necessary data is obtained through child studies to support the approval of a medication for children. A Pediatric Plan is a declaration of purpose outlining the kind of pediatric research (safety, effectiveness, pharmacokinetics/pharmacodynamics, etc.) that the applicant plans to undertake.[28]

US

Initiate pediatric studies and send in the information: Applicants may start pediatric drug and biologic studies for serious illnesses for whom there is currently no cure earlier. The information provided under PREA will vary depending on the type of application, product knowledge in pediatric populations, and the underlying illness or condition being treated.[28]

Preparing the Initial Pediatric Study Plan: An iPSP must be submitted by a sponsor who intends to submit a marketing application for a new active component, new indication, new dosage form, new dosing schedule, or new mode of administration

Create a study schedule for kids: Laws controlling the efficacy and safety of pharmaceuticals and biologics have existed since the early 1900s, but the inclusion of pediatric usage in drug labelling has been comparatively late.[28]

Timeline for initial PSP submission: If needed by PREA, a sponsor shall submit an iPSP no later than 60 calendar days following the date of the end-of-phase 2 meeting or at any other period mutually agreed upon by the sponsor and FDA. The sponsor shall submit the necessary evaluations or investigation by the deadline. In the event that a phase 3 trial, or a phase 2 and 3 study combined, is not planned, or is planned but will not fall under an IND, the sponsor must submit the iPSP no later than 210 calendar days prior to submitting a marketing application or supplement.[28]

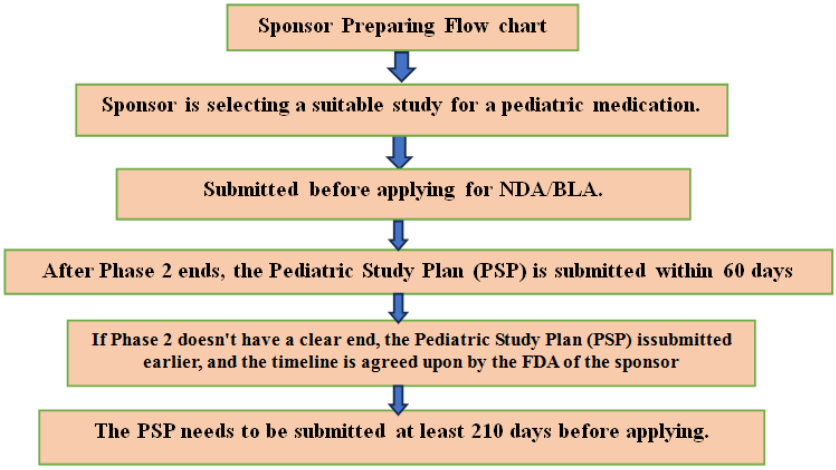

Figure 1: Flowchart of PSP approval process.

EU: The Paediatric Investigation Plan (PIP) is a research and development initiative designed to make sure the information needed is produced to establish the circumstances under which a pharmaceutical product might be approved for use in treating the pediatric population. The Paediatric Committee (PDCO) evaluates the PIP, and within the timeframes specified in Regulation (EC) No 1901/2006 (Paediatric Regulation), the Agency makes a decision.

Since the creation of pharmaceuticals is a dynamic process that depends on the findings of current research, there may have been some scientific ambiguity at the time the PDCO first evaluated the PIP. In most circumstances, this meant that more PIP modifications would have been required.

At the latest, after the Day 30 PDCO plenary debate, a decision regarding whether or not the PIP may be included in the pilot would be made. The applicant would be encouraged to submit a traditional PIP claim if the suggested approach is deemed to lack adequate scientific justification.[29,30]

Procedure for Pediatric Investigation Plan Registration and Approval in the EU

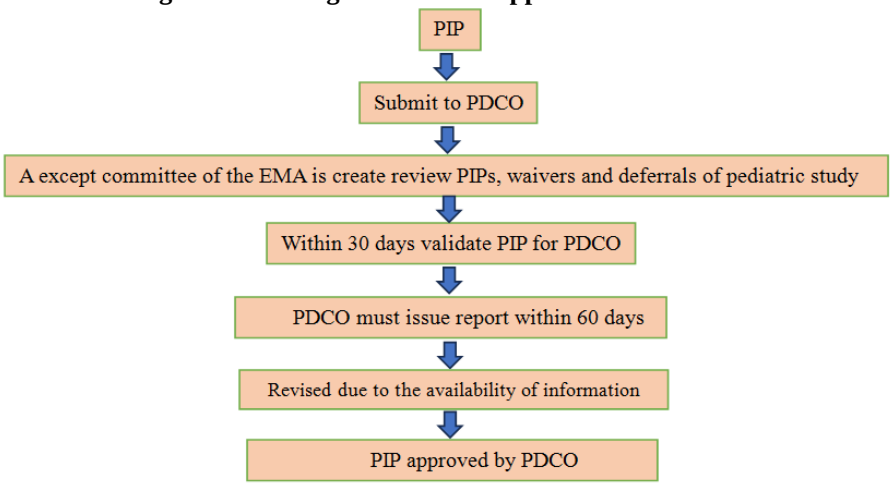

Figure 2: Approval process of PIP in EU.

INDIA: There are no special rules governing clinical studies in the pediatric population. Even in everyday practice, there are no exact standards for giving the pediatric dosage regimen. In order to harmonize with global compliances, the Central Drugs Standard Control Organization (CDSCO) must incorporate a paediatric drug development regulation into its ongoing organizational and restructuring of regulatory guidelines. This will produce more effective results without jeopardizing the safety of the population under discussion.[27]

Present state of pediatric research in India: Control India uses clinical trials and adult human subjects' procedures to develop pediatric drugs. No specific guidelines for the development of pediatric drugs exist. Inferences from adult dosages and safety and efficacy data from other industrialized nations are often utilized in Indian clinical practice. Healthcare professionals and caregivers have been forced to estimate doses (either for therapeutic use or for clinical trials) by crushing tablets, opening capsules, cutting tablets into quarters and halves, or proportionately reducing volume if the dose is liquid

due to a lack of guidelines specifically tailored for the pediatric population. This method of administering medication is challenging and may result in an incorrect dosage, which may raise safety issues (from overdosing) or reduce efficacy (from underdosing). It is incorrect to conflate children with tiny adults.[27]

Comparison of Pediatric Drug Development in USA, EU and India

PARAMETER	USA	EU	INDIA
Criteria for wavier	Ineffective or unsafe Pediatric studies are impracticable	Ineffective Unsafe	NO
Pediatric Definition	< 17 years	< 18 years	< 18 years
Protocol assistance	All scientific advice provided by FDA	Free scientific advice provided by FDA	NO
Market exclusivity for on-patent drugs	Provides 6 months of additional exclusivity	Regular products receive an additional 6 months of exclusive marketing, while orphan products are granted 2 years of exclusive marketing.	There are 7-8 years left from the drug approval date until the end of its patent life. Top of Form
Market exclusivity for off-patent drugs	No exclusivity	10 years exclusivity is available for off patent drugs	No exclusivity
Guidelines Specific to Pediatrics	Extensive and well-defined	Extensive and well-defined	Minimal and non-specific

CONCLUSION

Upon examination of global pediatric drug regulations, it becomes apparent that the pediatric population necessitates special considerations in medication prescribing due to their physiological immaturity. A review of international pediatric drug rules reveals that because of their physiological immaturity, children require extra care when prescribed medications. Strong rules are in place in the US and the EU, but India lacks standardized regulations. This creates problems like children not being able to take necessary medicines and drug abuse that causes unpleasant responses and resistance.

Specialized regulations for pediatric research in India need to be established immediately in order to address these important challenges. The initiatives of groups like the Indian Academy of Pediatrics highlight this necessity. This is proud of its large membership and unwavering dedication to improving the health and safety of children. These organizations are well-positioned to lead the way towards a future in which pediatric healthcare in India. It is distinguished by enhanced medication safety, efficacy, and accessibility, thereby guaranteeing better health outcomes for children across the country, through cooperative efforts to fortify pediatric regulation and research.

Funding: No funding was received for this study.
Conflict of Interest: The authors declare no conflict of interest.

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