Available online on 15 Dec, 2023 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with RAPS & Delhi Pharmaceutical Sciences & Research University


Review Article

Open Access

# A Comparative Review on the Regulatory Framework of Pediatric Drugs in the US and EU: Challenges and Recommendations

**V. Sri Sowmya*[a], Y.B Manjulatha [b], J. N. B Indusekhar [a], V. Bhaskar Raju [c]**

[a]*Assistant Professor, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andhra Pradesh, India 534101*
[b]*Professor, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andhra Pradesh, India 534101*
[c]*Principal and Professor, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andhra Pradesh, India 534101*

## Abstract

Children and adults have different pharmacokinetic and pharmacodynamic profiles, so it is necessary to confirm the drug's effects in pediatrics. Drugs utilised in paediatric research They are frequently referred to as "therapeutic orphans" since they are challenging to develop and lack adequate data. Therefore, it becomes necessary to study the optimal dosages and formulations in various age groups of children. The significance of pediatric rules emerged from the fact that the physiological conditions of adults and children are different, and the same dosing regimen cannot be recommended for both. The child protection in research was recommended at the Belmont report (1979) first time. The necessity for written informed consent of the subject from a legally authorized representative of a child was described in the Declaration of Helsinki (1964). The scarcity of available patient populations, practical complexities of research, and minimal financial returns have hampered pharmaceutical investment in the clinical studies for children. More recently, pediatric policy in the US and Europe have instituted a system of obligations and incentives to stimulate investment in the pediatric drugs development. These initiatives, in conjunction with a more sophisticated process of drug discovery and development, resulting in significant advancements in the labelling of drugs for pediatric use. The present study reviews the regulation of pediatric drugs in the USA, EU and recent updates concerned to their regulations. It discusses the pediatric clinical study plans, Incentives, Timelines, challenges and possible recommendations. The challenges include ethical issues, clinical trial designs, type of formulation preparation, dosing, bioavailability and drug response measuring techniques.

**Keywords:** BPCA, PREA, Pediatric study plan, Pediatric investigation plan, Pediatric clinical trials

**Article Info:** Received 13 Nov 2023; Review Completed 11 Dec 2023; Accepted 15 Dec 2023

**Cite this article as:**
Sowmya VS, Manjulathan YB, Indusekhar JNB, Raju VB, A Comparative Review on the Regulatory Framework of Pediatric Drugs in the US and EU: Challenges and Recommendations. Int J Drug Reg Affairs [Internet]. 2023 Dec 15 [cited 2023 Dec 15]; 11(4):74-86. Available from: http://ijdra.com/index.php/journal/article/view/635

**DOI:** 10.22270/ijdra.v11i4.635
*Corresponding author

## 1. Introduction

Children need specific medicines and approaches to drug development. They have different pharmacokinetic and pharmacodynamics responses as compared to adults. These variations are mostly brought on by differences in body water and serum protein composition in the children. It is necessary to study the drug profile in different age groups of children and drugs available for adult may cause adverse effects in children. back then, and unfortunately still today, numerous medicines were given in an “off label” manner to children, even without a license or marketing authorisation. Inadequate testing can result in direct risk of under or overdosing and a delayed risk of long-term adverse effects in children. Important medicines must be tested in each pediatric sub-population. The USA was the first country which made the act for pediatric clinical trials as the “FDA Modernization Act” (1997). After that the “Best Pharmaceuticals for Children Act” (BPCA, 2002) and the “Pediatric Research Equity Act” (PREA, 2003) were incorporated in the U.S. regulatory framework. The first joint pediatric regulatory action was taken with the issuance of ICH E11 guideline. (1,2)

### *Changes Occurring During Development and Age Groups*

Classification of pediatrics along with special feature of that age is given in Table 1. (3)

**Table 1.** Classification of pediatrics along with special feature of that age

| Age classification | Special feature |
|---|---|
| Preterm newborn infants | - Immature CNS<br>- Immature renal and hepatic clearance<br>- Unique spectrum of diseases and Uniqueresponse to treatment<br>- Small volume of blood |
| Term newborn infants (0 - 27 days) | - Volumes of distribution may vary<br>- Blood-brain barrier (BBB) is still developing<br>- Immature hepatic and renal clearance |
| Infants and toddlers (28 days - 23 months) | - Rapid mental, Physical and immune development<br>- Elimination of drugs from the body mayexceed that in adults |
| Children (2 - 11 years) | - Large variation and variability in development<br>- Onset of puberty varies and heralds a time of accelerated growth and marked change which may alter response to medications and doses required |
| Adolescents (12 to 16-18 years) | - Sexual maturation<br>- Rapid growth and ongoing neurocognitive development |

## 2. Pediatric Drug Regulations in the USA

In drug regulation, pediatric patients are defined as children younger than age 17. Example of pediatric cohorts:

- Neonates - birth to age less than 1-month
- Infants - age 1 month to less than 2 years
- Children - ages 2 to less than 12 years
- Adolescents - ages 12 to less than 17 years. (4)

***Regulating body***

FDA's "Office of New Drugs" (OND) in the CDER regulates the pediatric drugs. The "Office of Pediatric Therapeutics" (OPT) is mandated by Congress. Its primary mission is to assure access for children to innovative, effective and safe medical products. (5)

**Table 2.** USA Legislation and regulations with important pediatric drug regulation impact (6)

| Year | Legislation | Impact |
|---|---|---|
| 1997 | FDA Modernization Act | FDA could ask for pediatric trials. Additionally, 6 months marketing exclusivity is granted to the sponsors, if studies are done in pediatrics |
| 1998 | The Pediatric Rule | Required pediatric trials |
| 2000 | Children's Health Act | Established protections for children participating in the clinical studies |
| 2002 | Best Pharmaceuticals for Children Act | Reauthorized financial incentive to conduct pediatric trials. |
| 2003 | Pediatric Research Equity Act | Needs pediatric assessments |
| 2007 | Food and Drug Administration Amendments Act | Reauthorized BPCA and PREA |
| 2012 | Food and Drug Administration Safety and Innovation Act | Made BPCA and PREA permanent. Required neonatal expertise in Office of Pediatric Therapeutics |
| 2017 | FDA Reauthorization Act | Requires evaluation of oncology products based on molecular targets |
| 2017 | Research to Accelerate Cures and Equity for Children Act (RACE) | Updates PREA so FDA may now require pediatric assessments for oncology drugs when the molecular targets is substantially relevant to children's cancers. |

Best Pharmaceuticals for Children Act, which offers incentives but is voluntary, and the Paediatric Research Equity Act, which specifies requirements for paediatric development but does not provide incentives, are the two aspects of current legislation. Title V of FDASIA made both acts permanent in 2012 with few changes. (7)

***Best Pharmaceuticals for Children Act (BPCA)***

In August of 2017, the BPCA legislation was reauthorized by Congress, which renewed the NIH BPCA Program for five years. The new legislation also permits the NIH to prioritize research on the identification of biomarkers for pediatric diseases and conditions. (8) The overarching goals of the BPCA are:

- To encourage the pharmaceutical industries to perform pediatric clinical studies and to improve labeling for patented drug products used in children, by extending the patent's exclusivity for six months.

- For NIH to prioritize therapeutic areas, support clinical trials and other research, and to find off-patent medicinal products that require additional pediatric research. (9)

***Proposed Pediatric Study Request (PPSR) -***

It is a kind of draft written request (WR) outlining the clinical studies that will be needed to obtain the information required to improve the labeling of Pediatric drugs. (10) By presenting a PPSR, a sponsor can request the FDA to grant a WR. The PPSR should address different issues such as study objective, indication to be studied, type of clinical studies, study design, number of patients, inclusion/exclusion criteria, clinical endpoints, dosage forms, and formulation of the drug. (11,12)

***BPCA: Written Request (WR)***

Under BPCA, initiation of pediatric studies formally begins when FDA issues a WR to a drug sponsor to conduct pediatric studies for a particular drug. FDA may issue a WR upon reviewing the drug sponsor's PPSR. In deciding whether to grant the PPSR and to give a WR, FDA must determine if the planned research would provide information that could have a positive impact on health in children. Alternatively, FDA issues a WR on its own, requesting a company to voluntarily carryout the studies for all unapproved and approved indications for the medications that might be advantageous for children's health without having received a PPSR from the drug sponsor. It can be given for on and off-patent products. (13,14)

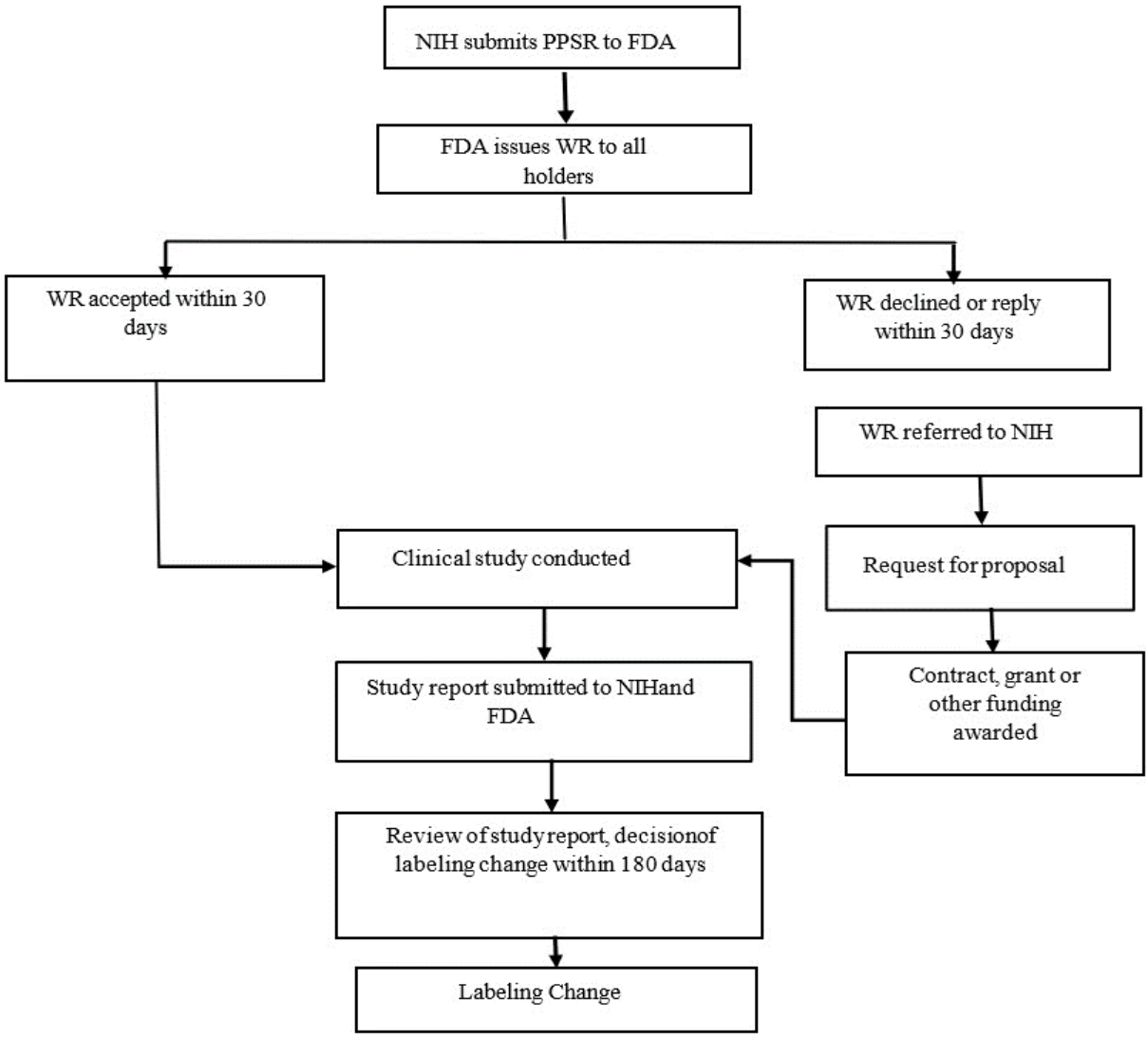


**Figure 1.** Workflow for the evaluation of off-patent drugs

***Basic Elements of a WR***

- Types and objectives of studies to be performed
- To study the indications
- Specified age groups and no. of patients to be studied; ethnic/minority representation
- Study endpoints, including pharmacokinetic, pharmacodynamic, safety, and efficacy endpoints
- Reporting of extraordinary (unexpected) findings
- Drug information, including dosage form,

administration route, regimen, need for age-appropriate formulation, and documentation requirements

- Statistical analyses to be performed
- Provisions for labeling (15)

***BPCA: WR Process for On Patent Drugs***

A PPSR may be submitted by a sponsor to OND Review Division seeking a WR from FDA. It should address every indication applicable to pediatrics and Proposed studies in all appropriate age groups. (14)

***BPCA: WR Process for Off Patent Drugs***

It established partnership between FDA and NIH to conduct studies on older, off-patent drugs to inform pediatric labeling. The request must be issued to all application holders – If declined by all holders of an application, NIH may complete studies. The procedure for submission, review and labeling of studies submitted by NIH is unique and outlined under section 409I of BPCA. (14)

The whole procedure is coordinated by the FDA and NICHD at the NIH, the current process isas follows and is given in Figure 1. (10)

***BPCA: Incentives***

BPCA establishes a voluntary incentive program through which a sponsor may gain the benefit of market protection (exclusivity) as a reward for having performed pediatric studies as specified in a WR from FDA. (16)

***Pediatric Marketing Exclusivity***

Exclusivity is granted only after -

- manufacturer completes and reports on the studies that had requested in writing,
- the studies include appropriate formulations of the drug for different each age groups, and
- any labeling changes that are approved—all within the agreed upon time frames.

According to the law, the manufacturer should suggest the labeling for children depending on the studies. Applicants for pediatric marketing exclusivity must submit, along with the report of requestedstudies, adverse event reports after post marketing regarding that drug. (17) Marketing exclusivity is an ADD-ON to existing exclusivity or patent protection. In general, products that don't have patent life or exclusivity is remaining cannot qualify. (18)

**Table 3.** List of underlying incentives and its pediatric exclusivity. (18)

| Underlying Incentive | Type of Innovator Applications Eligible for Underlying Incentive | Market Protection if Pediatric Exclusivity Is Earned |
|---|---|---|
| Patent protection | NDA | Patent life + 6months |
| NDA exclusivity | NDA | 5 years + 6 months |
| New conditions of use exclusivity | NDA | 3 years + 6months |
| Exclusivity of Orphan drugs | NDA, BLA | 7 years + 6 months |
| Biologic product exclusivity | BLA | 12 years + 6 months |
| Timeline for submission of biosimilar product application | BLA | 4 years + 6 months |

**Table 4.** Examples of the some of the drugs that granted Pediatric exclusivity in 2021. (19)

| Drug | Date of Exclusivity | Sponsor | Indication(s) |
|---|---|---|---|
| Dabigatran | 2/12/2021 | Boehringer Ingelheim | Venous thromboembolism (VTE) |
| Deutetrabenazine | 5/5/2021 | Teva | Tourette syndrome |
| Exenatide | 4/1/2021 | AstraZeneca | Type 2 diabetes mellitus |
| Ferric Oxyhydroxide | 6/1/2021 | Vifor Fresenius Medical Care | Lowering serum phosphorus levels in patients with CKD and hyperphosphatemia |
| Fluticasone & Fluticasone/Salmeterol | 6/10/2021 | Teva | Persistent asthma |
| Glecaprevir/Pibrentasvir | 5/18/2021 | AbbVie | Chronic hepatitis C virus (HCV) infection |
| Halobetasol | 5/21/2021 | Mayne | Plaque psoriasis |

***Pediatric Research Equity Act (PREA)***

For a few medicines and biological products, PREA mandates the study of pediatric research. In particular, PREA mandates that pediatric assessments be incorporated in NDAs and BLAs for new pharmaceutical ingredients, new dosage formulations, new dosing regimen, new indications and administration routes unless the manufacturer has secured a waiver or deferral. (20) Any product development program covered by PREA must

submit an "initial Paediatric Study Plan" (iPSP). The PSP's goal is to identify necessary pediatric studies as early in the product development and to start planning for these studies. Any marketing application subjected to PREA requires the submission of an agreed initial Paediatric Study Plan. (7)

***Pediatric Review Committee (PeRC)***

The PeRC is a closed committee established under the "FDA Amendments Act" to hold out activities concerning BPCA and PREA. To help ensure quality and consistency, the PeRC offers the framework for the preparation of consultations and general reviews of pediatric information in pediatric plans, assessments, and research. It reviews all WRs, waivers, deferrals, and studies are submitted in response to a WR. (12)

***Pediatric Study Plan (PSP)***

The iPSP's goal is to identify necessary pediatric studies early in the drug development and begin planning for those studies.

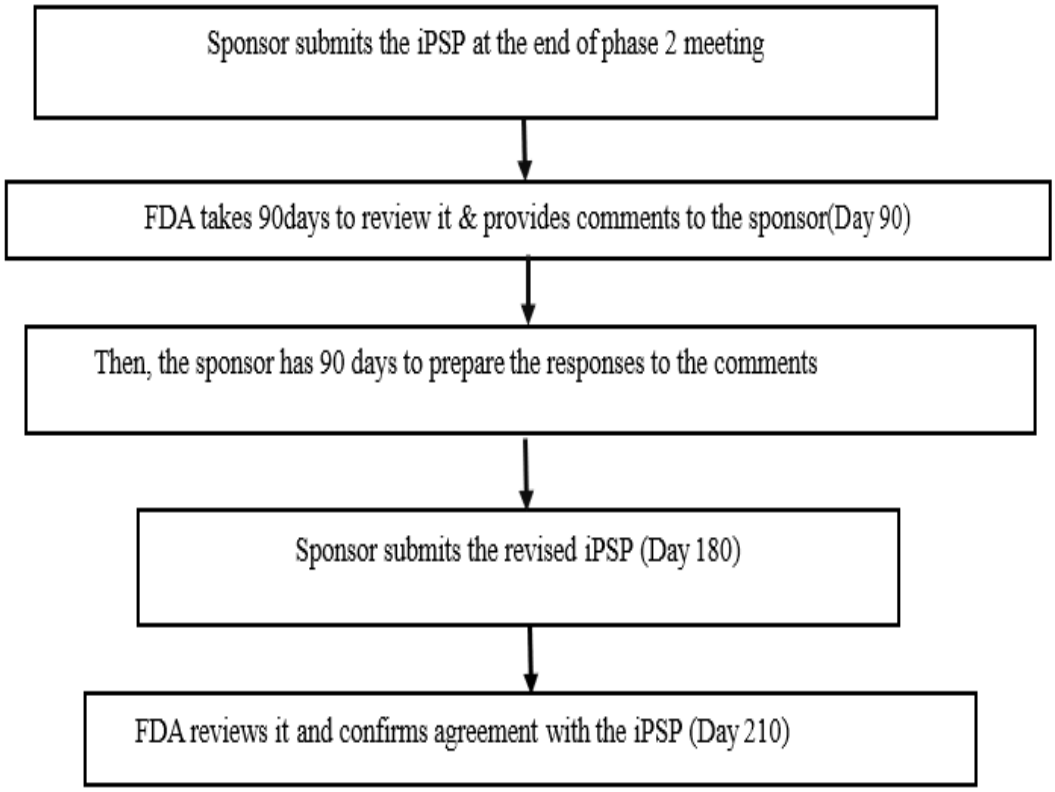


**Figure 2.** Timelines for PSP submission

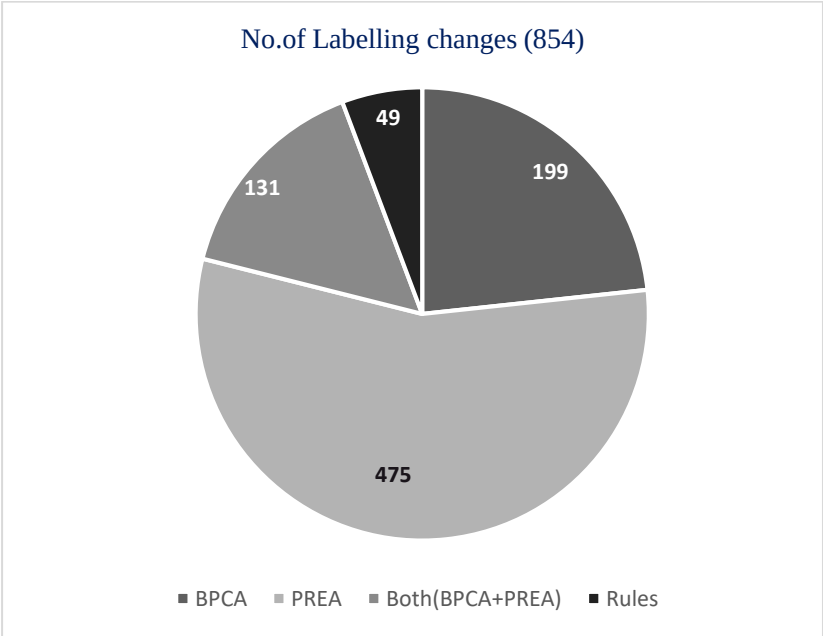


**Figure 3.** Pie-chart representation of No. of labeling changes until 2020 (April)

The statistical representation of number of labeling changes under BPCA, PREA, both (BPCA+PREA) and pediatric rule as of April 2020 is given in below pie-chart (figure 3). (21)

***The procedure for approving pediatric drugs in the US***

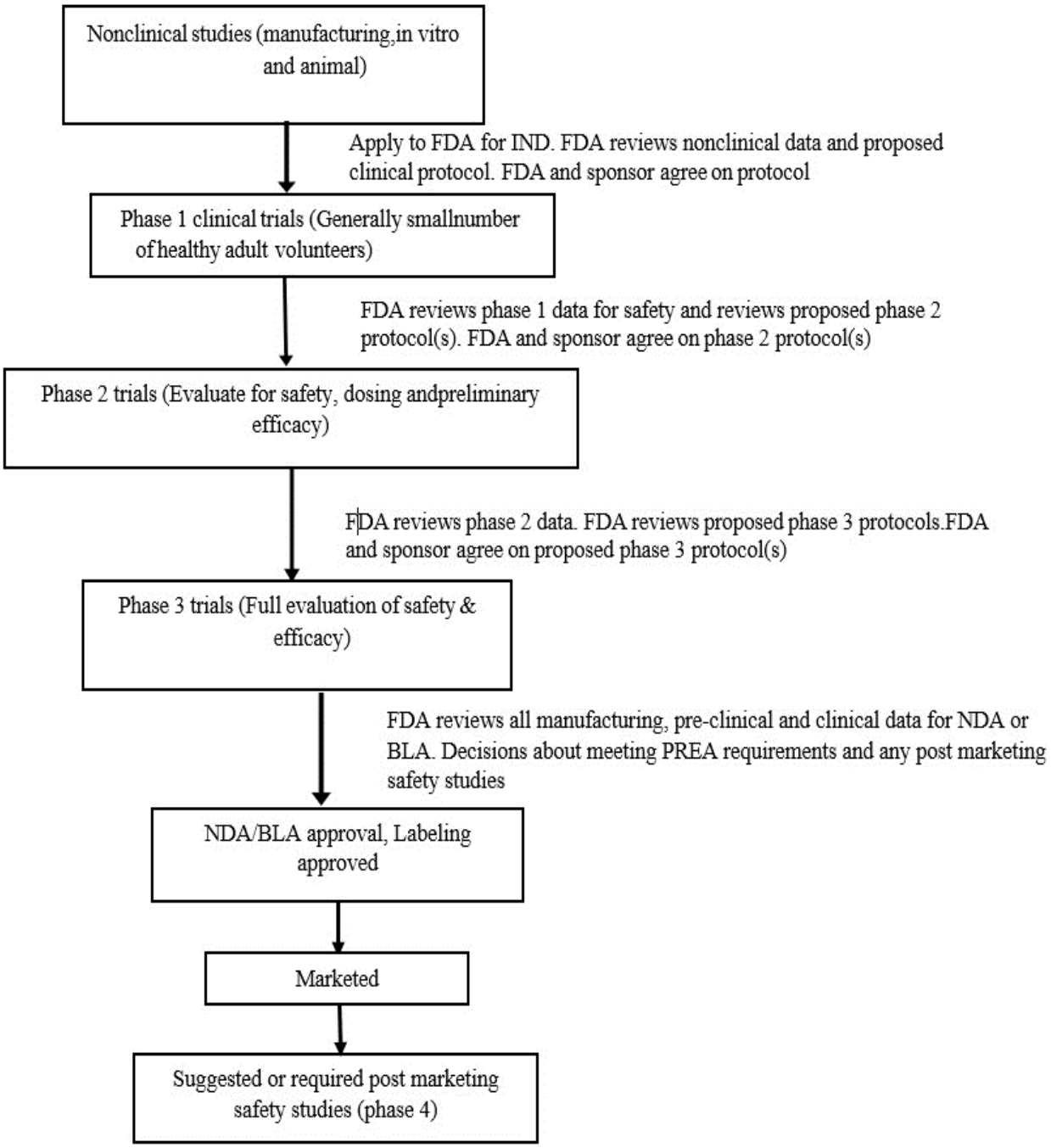


**Figure 4.** The Pathway of pediatric drug approval in the US

***Pediatric Advisory Committee (PAC)***

Additionally, for 18 months following the FDA's approval of labeling changes, US law necessitates a pediatric-focused safety evaluation by the Paediatric Advisory Committee (PAC) for studies done under the BPCA or PREA. (7)

***Statistics***

The statistical representation of Pediatric Labeling Changes from 1998 to 2019 is given in figure 5. (22)

**3. Pediatric Drug Regulations in the EU**

The paediatric population is defined as the population between birth to 18 years of age in EU. It encompasses several subsets.

- term and post-term neonates: from the birth date plus 27 days;
- infants (or toddlers): from 1 month (28 days) to 23 months;
- children: from 2 years to 11 years; and
- adolescents: from 12 years to <18 years. (23)

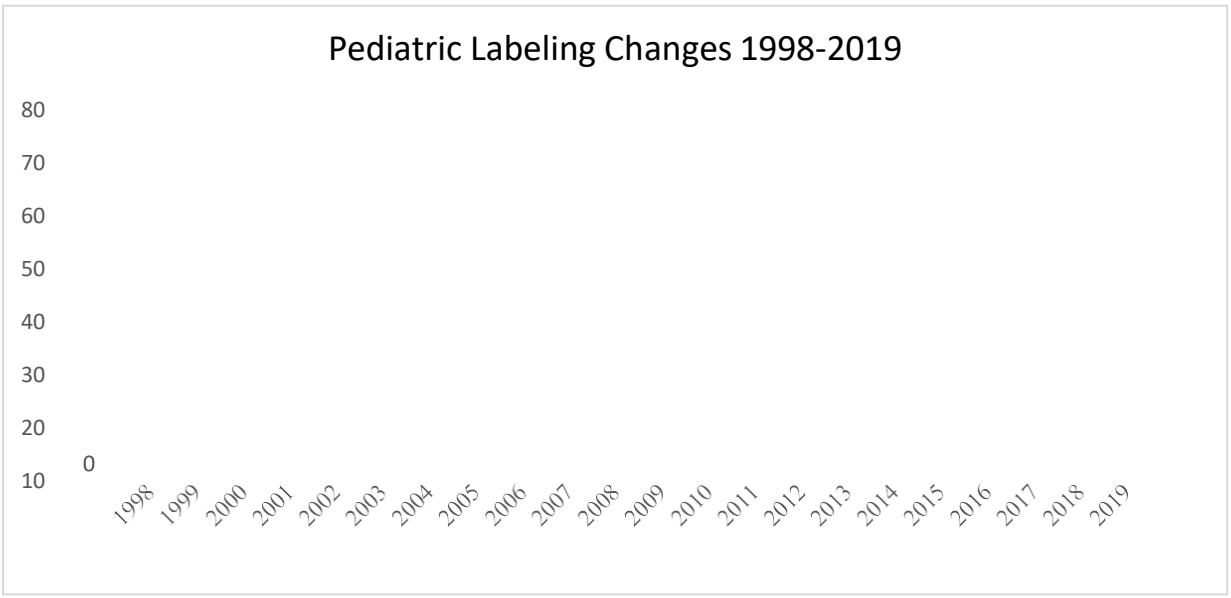


**Figure 5.** Statistical representation of No. of labeling changes from 1998 to 2019

***Current regulatory framework***

The "Paediatric Regulation" (Regulation EC No 1901/2006 of the European Parliament and of the Council, revising Regulation EEC No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC, and Regulation EC No 726/2004) came into effect on January 26 of 2007. (24) The Pediatric Regulation established a unified system of pediatric obligations and incentives to aid the evaluation of newly authorized drugs covered by a Supplementary Protection Certificate (SPC). The SPC extends the patent's term to make up for the time lost between the filing of an application and granting of the first marketing license in Europe. "Pediatric investigation plan" (PIP) applications are required to be sent to the EMA after finishing the adult human pharmacokinetic studies, for newly approved products. When the clinical studies are finished as agreed in the PIP, new pharmaceuticals covered by SPC may be given a 6-month extension. Additionally, it provided a voluntary development pathway leading to a "Paediatric Use Marketing Authorization" (PUMA) for off-patent drugs that may have a pediatric use. (10)

***Pediatric Committee (PDCO)***

The Pediatric Committee is the EMA's scientific committee responsible for all of activities pertaining to children's medications and supports the growth of such medications by defining pediatric requirements and providing scientific expertise. (25)

***Paediatric Investigation Plan (PIP)***

It is a development strategy aimed at ensuring that the information supports the authorization of a medicine is gathered through research on children. (26)

**Table 5.** List of documents required in the Structure of PIP application. (27)

| S.No. | Sections | Description | Format |
|---|---|---|---|
| 1. | Section A | Product and Regulatory information | PDF form |
| 2. | Section B | Targeted conditions / indications andneeds General pharmacology, Clinical need by age groups/subsets (with prevalence), Benefit of the product versus alternatives | Word document, freeformat |
| 3. | Section C | Waiver request | Word document, freeformat |
| 4. | Section D | Summary of existing data and Development plan Quality, Non- clinical, Clinical (±Risk managementPlan), synopses of proposed non-clinical and clinical research | Word document, free format |
| 5. | Section E | Timelines, deferral request | Word document, free format |
| 6. | Key elements form: applicant's proposal for opinion | | PDF form |

***Evaluation and timeline procedures for PIP***

Once the applicant submits an 'intent to file', the PDCO will appoint a 'rapporteur' to lead the assessment and a 'peer reviewer' to check the assessment's quality from within the Committee. The rapporteur and peer reviewer check the initial PIP and present their findings to the PDCO. The review process takes 120-days; however, there is also a pause (clock stop) at Day 60 that allows the PDCO to ask questions of the applicant. These clock stops are usually a maximum of three months long, although the length is agreed upon with the PDCO on a case-by-case basis. (28)

***Pediatric Investigation Plan: Assessment Procedure*** *(28)*

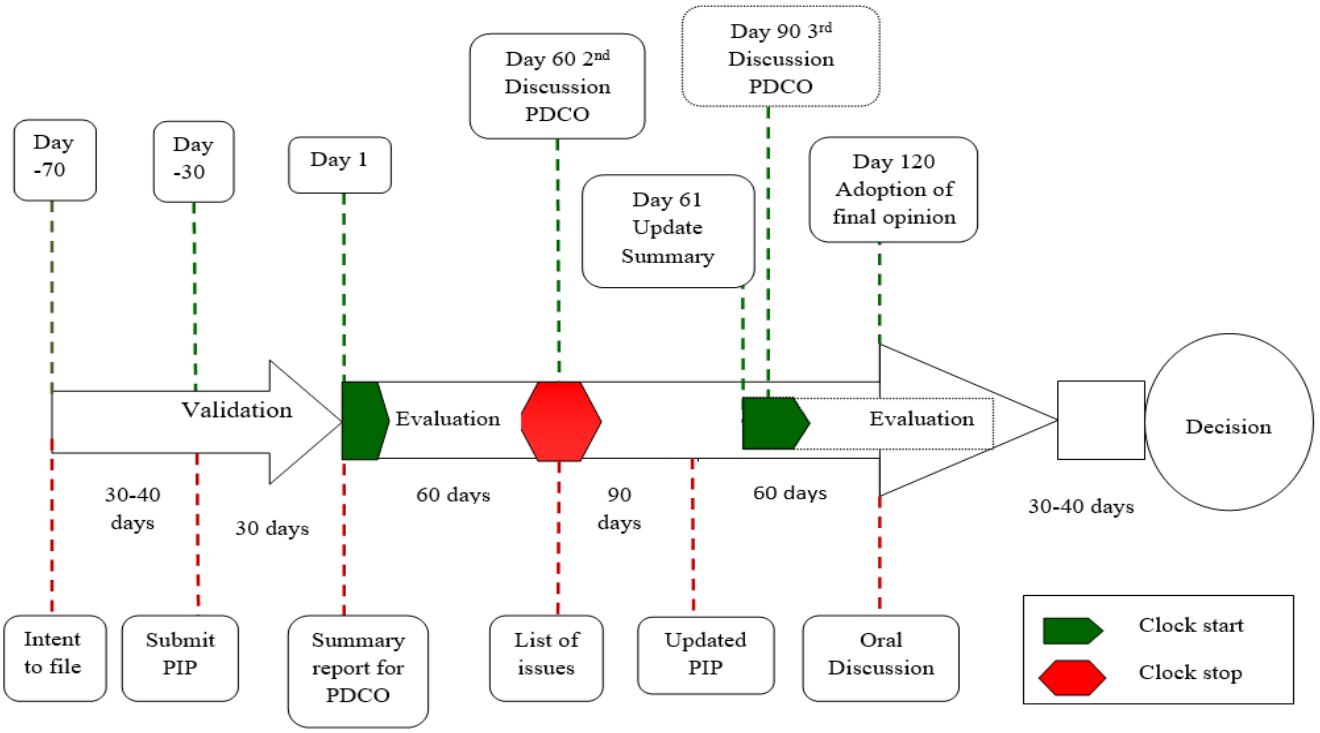


**Figure 6:** Paediatric Investigation Plan: Assessment Procedure

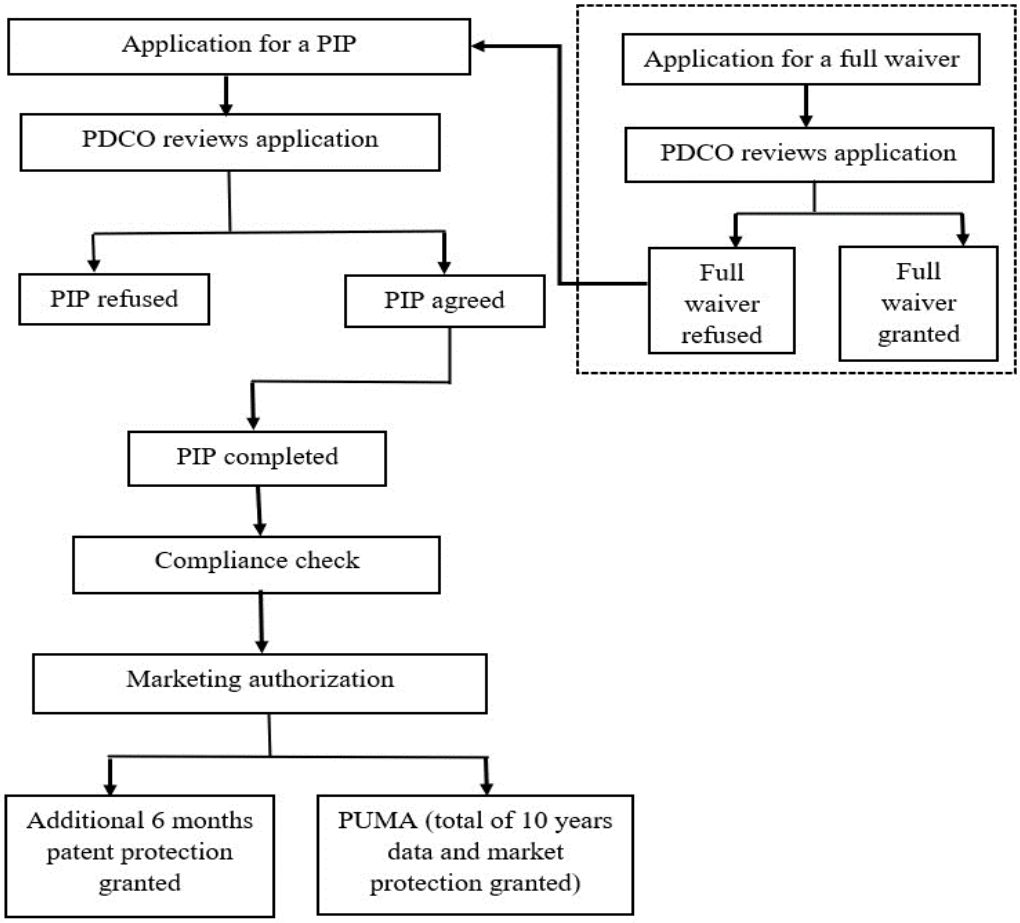


**Figure 7.** The approval pathway of Pediatric drugs in the EU *(29)*

***Paediatric Use Marketing Authorisation (PUMA)***

These are issued by the EMA for medications that are exclusively for pediatric use, that is, for use in patients younger than 18 years. Like ordinary EMA marketing authorisations, a PUMA approval is valid in all countries of the European Economic Area. The PUMA must follow a PIP, agreed by the PDCO. Due to this reason, the data used for PUMA approved drugs are protected for 10 years, and the applications are partially exempt from fees. (30,31) The Pediatric Regulation introduced this authorisation for medicines that are: already approved drugs; not protected by an SPC or patent that meets the criteria for an SPC; and solely intended for pediatric use.

***Paediatric Use Marketing Authorisation (PUMA)***

These are issued by the EMA for medications that are exclusively for pediatric use, that is, for use in patients younger than 18 years. Like ordinary EMA marketing authorisations, a PUMA approval is valid in all countries of the European Economic Area. The PUMA must follow a PIP, agreed by the PDCO. Due to this reason, the data used for PUMA approved drugs are protected for 10 years, and the applications are partially exempt from fees. (29,30) The Pediatric Regulation introduced this authorisation for medicines that are: already approved drugs; not protected by an SPC or patent that meets the criteria for an SPC; and solely intended for pediatric use

**Table 6.** List of medications that are granted PUMA till now (32-37)

| Productname | Company name | International non-proprietaryname (INN) | Indication | Exclusivity granted date |
|---|---|---|---|---|
| Buccolam | ViroPharma SPRL | Midazolam | Epilepsy | 04/09/2011 |
| Hemangiol | Pierre FabreLaboratories | Propranolol | Infantile Hemangioma | 23/04/2014 |
| Sialanar | Proveca PharmaLimited | Glycopyrronium | Sialorrhea | 15/09/2016 |
| Alkindi | Diurnal Ltd. | Hydrocortisone | Adrenal Insufficiency | 09/02/2018 |
| Kigabeq | ORPHELIA Pharma SAS | Vigabatrin | Infantile spasms (West's syndrome) & Partial Epilepsy | 20/09/2018 |
| Slenyto | RAD Neurim PharmaceuticalsEEC SARL | Melatonin | Insomnia andAutistic Disorder | 20/09/2018 |

***Statistics*** *(38)*

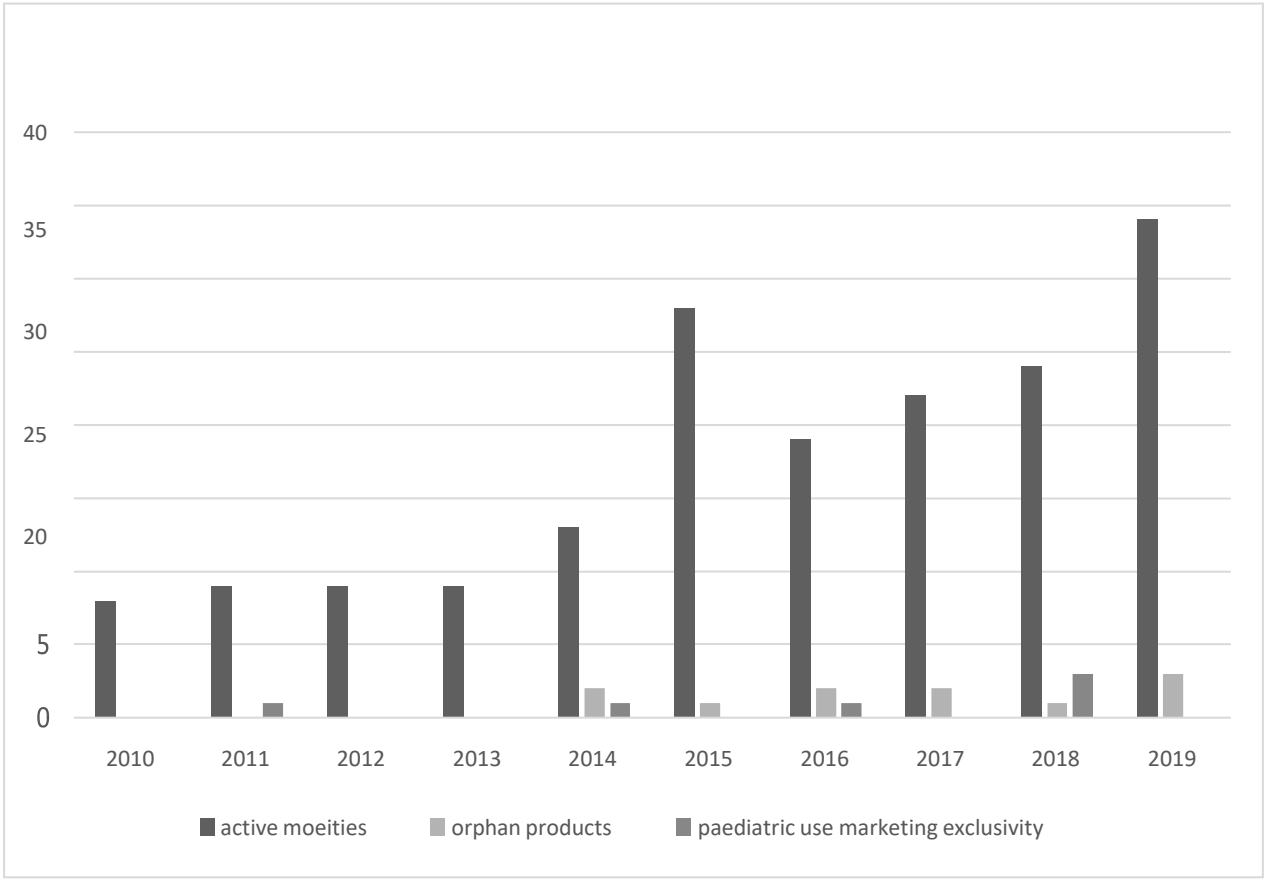


**Figure 8.** Graphical representation of no. of active moieties, orphan products and pediatric use marketing exclusivity products approved in the EU

**4. Comparison of Pediatric Drug Regulations in the US and EU**

**Table 7.** Comparison of Pediatric Drug Regulations in the US and EU.

| Parameter | US | | EU |
|---|---|---|---|
| **Legislation** | **FDA BPCA/FDASIA 2012** | **FDA PREA/FDASIA 2012** | **EU–EMA (Regulation1901/2006)** |
| Applies to | Incentives | Requirements | Incentive and requirements |
| which age to cover | All relevant paediatric populations (birth to 16 years). | All relevant paediatric populations (birth to 16 years). | All the paediatric population's groups(birth to 18 years). |
| Products included in obligations | All medicines | New medicines and biosimilars | New medicines; authorized products under patent/SPC |
| Orphan-designateddrugs | Included | Excluded | Included |
| Development of Pediatric drugs | Optional | Mandatory | Mandatory |
| Plan | WR | PSP | PIP |
| Template/content | PPSR template pertaining to rationalefor studies; study design; and formulations FDA will use the PPSR to draft the WR | PSP-Up to 60 pagesOverview of disease/ product, outline/ plans of pediatric studies, background supporting data (adult), waiver/ deferral requests, formulation, timelines, agreements | PIP-Should be a maximum 40 pages Administrative and product information; Info on disease and therapeutic benefit; Application for a waiver if applicable; Proposed pediatric development plan; |
| Timing of submission | Anytime | End of phase 2 studies | End of phase 1 studies |
| Main reward | 6-months patent extension | None | 6-months SPC extension& 2- year extension for orphan drugs |

**5. Challenges & Recommendations involved in the development of Pediatric Drugs**

Due to numerous obstacles, the development of pediatric drugs has been overlooked by the pharmaceutical industry. (39)

***Ethical issues***

The complex process of conducting PCTs includes many ethical considerations related to pediatric clinical research. Since children cannot legally give their own consent, the issue of "informed consent" in PCTs is extremely complicated. (39)

**Recommendation:**

Patients who are under legal age must have "informed consent" given by a parent or other legal representation. Experienced investigators must provide the information while applying no pressure and giving the parents or legal representative ample time to consider it. (39) Capability to integrate an "Electronic informed consent form" (eICF) solution App in the similar device, that offers an easy-to-understand consent form, with audio of the approved consent in the patient's language and embedded information for specified concepts. (40)

***Distress and discomfort in trial procedures***

Given the sensitivity of pediatric patients, extra care should be taken to reduce any suffering or discomfort that children may endure during trial-related operations. Taking all reasonable precautions to prevent needless suffering is a crucial ethical consideration while designing a PCT. (39)

***Recommendation:***

In any instance, age-appropriate validated measures must be used to measure any signs of uneasiness, pain, or distress. Where the procedures result in a certain level of pain, appropriate analgesia should be administered. (39)

***Enrolment of patients and retention***

The enrolment of children into clinical trials is challenging due to relatively small number of available participants. Patient retention is a key factor to ensuring clinical trial success. Retention of patients throughout the entire cycle of a clinical studies is vital from a scientific, and economic, point of view. Poor retention negatively impacts the integrity of evaluable data and increases costs by imposing delays for pharmaceutical companies. (39-42)

***Recommendation:***

Customized communication is a vital part of mitigating risks in every stage of a pediatric studyand helps build trust. Trust and close relationships between site staff, parents, and children are major factors to give consent for the children in participating clinical studies and stay compliant throughout the trial. Educating and engaging parents, younger study participants can change the negative attitudes about research and decrease parents' worries about disruption to their daily lives. (43)

***Dropouts***

The reason for children to reject participation in the study was that they had to undergo procedures that were scary or painful, such as injections or blood draws. In other cases, the required time commitment for traveling to the study site for evaluations interfered with other

activities the children preferred. (42)

***Recommendation***

Home health visit personnel employ a no. of techniques to mitigate children's fears and engage them as partners in the process:

- Age-appropriate tools
- Smallest needle gauge possible for a particular patient (one size doesn't fit all)
- Sensory devices (e.g., Buzzy® shotblocker)
- Alternative sampling techniques (e.g., finger or heel pricks, salivary samples). (42)

***Designing of clinical trials***

The planning stage is crucial for the quick and efficient conduct of clinical studies. As a result, it requires an endless amount of background research, logical thinking, and familiarity with the potential hazards and consequences. (39)

***Recommendation: Innovative design of clinical trials***

Innovative techniques for designing clinical trials are very effective and suitable for addressing Pediatric clinical trial difficulties associated with a low no. of patients and control groups. (39) To make pediatric patients willing to provide data throughout the study, clinical trial stakeholders should turn to engaging playful designs. The questions must seem appealing; colors and animated images should be integrated. The newest generation is more comfortable with advanced technologies than the older one, and is expected that utilizing electronic devices to collect clinical data will enhance the compliance. (40)

***Regulatory process***

Distinct countries and investigation sites may have extremely distinct and lengthy regulatory approval processes and timelines. This procedure has a significant drawback when it comes to multi-center international research because it may result in different versions of the study protocol that will need to be modified further to be consistent throughout the investigation sites. (39)

***Recommendation: Engage with Regulators Effectively***

After collaborating with stakeholders and thinking carefully about data choices, a final and crucial recommendation for industry sponsors is to meet early and effectively with the FDA. Too often sponsors perceive their regulatory interactions as fraught and struggle to understandwhen and how to engage with the FDA, EMA and other regulatory agencies. In the European context, the new Regulation on Clinical Trials envisions the introduction of a centralized system of submissions to quicken and harmonize the regulatory approval process of clinical studies within the EU. Companies should reframe their engagement as a team effort in which all stakeholders are united in wanting to advancethe best therapeutics for children. (39,44)

To do so, sponsors should:

- Start discussions early
- Come to discussions prepared
- Ensure that plans for all regulatory entities are consistent. (44)

***Drug Formulation:***

The development of age-appropriate and acceptable paediatric dosage forms is a complex and challenging process, as it is necessary to have in consideration children´s acceptability and preferences for different formulations and to understand the physical and biochemistry differences between children and adults. Acceptability of medicines in children and caregivershave an important impact on therapeutic adherence and consequently on the safety and efficacy. Factors that could impact the acceptability of a medicine during new dosage form design are: palatability and swallowability, appearance, complexity of administration, the dose required, frequency of dosing and treatment duration, the administration device the containers closure system, administration route. (45)

***Recommendation:***

Design of pediatric oral dosage forms should consider differences from adults like swallowing abilities, taste preferences and dosage requirements. For years, liquid formulations were preferred for children as they allow to adjust doses across age groups. However, new oral formulations have been considered and recommended for children, namely orodispersible tablets and tablets used to prepare oral liquid preparations suitable for younger children, granules, multi-particle dosage forms, mini-tablets and pellets Innovative collaborative research, additional funding opportunities and new regulations have shown little progress in the formulation of pediatric drugs. A paradigm shift towards oral solid formulations and focusing on innovative preparations, such as flexible, dispersible, and multi-particulate oral solid dose forms, are some of these advancements. (46)

## 6. Conclusion

The health authorities in the US and EU exhibit a strong commitment to expand access to pediatric medications. Beginning from the development process, pharma companies should focus on pediatric concerns, including both potential toxicity problems and pediatric formulations and also acquiring adult data that can aid with pediatric programming. Clinical trial networks like "The European Network of Paediatric Research, c4c, I-ACT" in the US and Europe have joined together to build the capacity for global pediatric studies. All stakeholders involved in the development process, comprising but not restricted to academia, industry, patient and disease groups, regulatory agencies, and ethics committees must work collaboratively. In the long term, statutory and regulatory incentives in the US and Europe may help to establish a global pediatric research infrastructure with a sufficient economy of scale and performance to permit pediatric medicine development to become a sustainable sector of the drug and biological products industry.

**Acknowledgements**

We would like to express our sincere gratitude to Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, affiliated to Andhra University, Visakhapatnam, Andhra Pradesh, India.

***Financial Disclosure statement:*** The author received no specific funding for this work.

**Conflict of Interest**

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

**References**

1. Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: The Impact of Evolving Regulations. Advanced Drug Delivery Reviews. 2014;73:2–13. doi:10.1016/j.addr.2014.02.003
2. Ajay S, Vikaas B, Manjusha C. A comprehensive study on regulation on clinical trials of Pediatrics in US, EU and India [Internet]. Akinik Publications; 2016 [cited 2023 Nov 26]. Available from: https://www.thepharmajournal.com/archives/?year=2016&vol=5&issue=10&ArticleId=877
3. Shikha S, Divya S, Nishi S. Role of regulatory bodies in pediatric products and pediatric drug exclusivity with special reference to US, Europe and Japan. Int J AdvRes (Indore). 2015;3(3):1104-1111. Available from: https://www.journalijar.com/uploads/93_IJAR-5340.pdf .
4. Office of New Drugs Module [Internet]. FDA [cited 2023 Nov 26]. Available from: https://www.accessdata.fda.gov/scripts/cderworld/index.cfm?action=newdrugs%3Amain
5. Office of Pediatric Therapeutics [Internet]. [cited 2023 Nov 26]. Available from: https://www.fda.gov/about-fda/office-clinical-policy-and-programs/office-pediatric-therapeutics
6. Baum VC, Bax R, Heon D, Yang Z, Sakiyama M. Pediatric drug regulation: International perspectives. Pediatric Anesthesia. 2019;29(6):572–82. doi:10.1111/pan.13638
7. Penkov D, Tomasi P, Eichler I, Murphy D, Yao LP, Temeck J. Pediatric medicine development: An overview and comparison of regulatory processes in the European Union and United States. Therapeutic Innovation & Regulatory Science. 2017;51(3):360–71. doi:10.1177/2168479017696265
8. The Federal Register [Internet]. Federalregister; 2019 [cited 2023 Nov 26]. Available from: https://www.federalregister.gov/documents/2019/04/23/2019-08167/best-pharmaceuticals-for-children-act-bpca-priority-list-of-needs-in-pediatric-therapeutics
9. Best Pharmaceuticals for Children Act - BPCA [Internet]. U.S. Department of Health and Human Services [cited 2023 Nov 26]. Available from: https://www.nichd.nih.gov/research/supported/bpca
10. Schwarz S. Make off-patent drugs available to children: Regulatory approaches in Europe and the US [Internet]. [cited 2023 Nov 26]. Available from: https://www.dgra.de/media/pdf/studium/masterthesis/master_schwarz_s.pdf
11. US Food & Drug Administration. Lynne, Y. Pediatric Drug Development RegulatoryConsiderations [Internet]. [cited 2023 Nov 26]. Available from: https://www.fda.gov/media/100571/download
12. Gadge PM, Kenjale PP, Pokharkar VB, Gaikwad VL. Global Pediatric Regulations: An overview. Therapeutic Innovation & amp; Regulatory Science. 2019; 216847901986409. doi:10.1177/2168479019864090
13. Pediatric Drug Research: Studies Conducted under Best Pharmaceuticals for Children Act. 2007 [Internet]. [cited 2023 Dec 3]. Available from: https://www.govinfo.gov/content/pkg/GAOREPORTS-GAO-07- 557/html/GAOREPORTS-GAO-07-557.htm .
14. Khurana M. Pediatric Drug Regulation. 2018; [Internet]. US FDA;2018 [cited 2023 Dec 3]. Available from: https://cersi.umd.edu/sites/cersi.umd.edu/files/Khurana_Pediatric%20Drug%20Regulation.pdf.
15. Field MJ, Boat TF. Safe and effective medicines for children pediatric studies conducted under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Washington: National Academies Press; 2012.
16. Center for Drug Evaluation and Research. Best Pharmaceuticals for Children Act (BPCA) [Internet]. FDA; [cited 2023 Dec 3]. Available from: https://www.fda.gov/drugs/development-resources/best-pharmaceuticals-children-act-bpca.
17. Susan T. FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe andEffective [Internet]. FAS; 2012 [cited 2023 Dec 3]. Available from: https://fas.org/sgp/crs/misc/RL33986.pdf
18. Center for Drug Evaluation and Research. Qualifying for pediatric exclusivity under Section 505A of the federal [Internet]. FDA; 2022 Mar 01 [cited 2023 Dec 3]. Available from: https://www.fda.gov/drugs/development-resources/qualifying-pediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently
19. Pediatric Exclusivity Granted List June 2021 [Internet]. FDA; 2023 May [cited 2023 Dec 3]. Available from: https://www.fda.gov/media/132652/download .
20. Center for Drug Evaluation and Research. How to comply with the Pediatric Research Equity Act [Internet]. FDA; 2005 Sept [cited 2023 Dec 3]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/how-comply-pediatric-research-equity-act
21. US Food & Drug Administration. New Pediatric Labeling Information Database. [Internet]. FDA; 2023 Dec [cited 2023 Dec 15]. Available from: https://www.accessdata.fda.gov/scripts/sda/sdnavigation.cfm?sd=labelingdatabase
22. US Food & Drug Administration. FDA OVERVIEW OF THE PEDIATRIC LEGISLATION [Internet]. FDA;2019 Nov 21 [cited 2023 Dec 3]. Available from: https://www.fda.gov/media/132890/download .
23. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations IV: Paediatric population. [Internet]. EMA; 2018 [cited 2023 Dec 3]. Availablefrom: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good- pharmacovigilance-practices-gvp-product-population-specific-considerations-iv_en-0.pdf .
24. Guideline on pharmaceutical development of medicines for paediatric use. [Internet]. EMA; 2013 [cited 2023 Dec 3] Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf .
25. Paediatric Committee (PDCO) - European Medicines Agency. [Internet]. EMA [cited 2023 Dec 3]. Available from: https://www.ema.europa.eu/en/committees/paediatric-committeepdco#:~:text=The%20Paediatric%20Committee%20(PDCO)%20is,expertise%20and%20defining%20paediatric%20needs
26. Paediatric investigation plans - European Medicines

Agency. [Internet]. EMA [cited 2023 Dec 3]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans
27. Tomasi P. Key concepts of the paediatric regulation and latest developments [Internet]. EMA [cited 2023 Dec 3]. EMA. Available from: https://www.ema.europa.eu/en/documents/presentation/presentation-key-concepts- paediatric-regulation-latest-developments-paolo-tomasi_en.pdf .
28. Paediatric medicine: Paediatric Investigation Plan. [Internet]. EMA [cited 2023 Dec 3]. Available from: https://toolbox.eupati.eu/resources/paediatric-medicine-paediatric-investigation-plan/ .
29. Faulkner B, Delgado-Charro MB. Cardiovascular Paediatric Medicines Development: Have Paediatric Investigation Plans Lost Heart? Pharmaceutics. 2020;12(12):1176. doi:10.3390/pharmaceutics12121176
30. Paediatric-use marketing authorisation [Internet]. Wikipedia [cited 2023 Dec 3]. Available from: https://en.wikipedia.org/wiki/Paediatric-use_marketing_authorisation
31. Paediatric-use marketing authorisations - European Medicines Agency [Internet]. [cited 2023 Dec 3].Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/paediatric-medicines/paediatric-use-marketing-authorisations#:~:text=The%20PUMA%20was%20introduced%20by,developed%20fo r%20use%20in%20children.
32. Buccolam - European Medicines Agency [Internet]. EMA; 2011 Sept 19 [cited 2023 Dec 3]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/buccolam#authorisation- details-section .
33. Hemangiol - European Medicines Agency [Internet]. EMA; 2014 May 19 [cited 2023 Dec 3]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/hemangiol .
34. Sialanar - European Medicines Agency [Internet]. EMA; 2016 Sept 29 [cited 2023 Dec 3]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/sialanar
35. Alkindi - European Medicines Agency [Internet]. EMA; 2018 Mar 01 [cited 2023 Dec 3]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/alkindi
36. Kigabeq - European Medicines Agency [Internet]. EMA; 2023 Jul 07 [cited 202 3 Dec 3]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kigabeq
37. Slenyto - European Medicines Agency [Internet]. EMA; 2011 Sept 19 [cited 2023 Dec 3]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/slenyto
38. Medicines for children - Public Health - European Commission. [Internet]. EMA; 2020 [cited 2023 Dec 3]. Available from: https://ec.europa.eu/health/human-use/paediatric-medicines_en
39. Chiaruttini G, Felisi M, Bonifazi D. Challenges in paediatric clinical trials: How to make it feasible. The Management of Clinical Trials;2018. doi:10.5772/intechopen.72950
40. Overcoming the Complexities of Pediatric Clinical Trials - Kayentis [Internet]. Kayentis; 2020 Apr 02 [cited 2023 Dec 3]. Available from: https://kayentis.com/overcoming-the-complexities-of-pediatrics-clinical-trials/
41. Hanumante NM, Ransubhe SP. Recruitment of babies in vaccine trial: A challenge. Indian J Child Health. 2019; 6(8):424-7. Available from: https://mansapublishers.com/IJCH/article/view/1721 .
42. Effectively Addressing the Challenges of Pediatric Clinical Trials with Patient CentricBest Practices [Internet]. [cited 2023 Dec 3]. Available from: https://www.firmaclinicalresearch.com/wpcontent/uploads/2019/11/Firma_WhitePaper _Pediatric_update_v3.pdf .
43. 3 Steps to Effective Pediatric Recruitment and Retention [Internet]. [cited 2023 Dec 3]. Available from: https://prahs.com/insights/3-steps-to-effective-pediatric-recruitment-and-retention .
44. Christoph H, Michael C, Jennifer C, Julia V, Lindsay S. Plan and Design with the Childin Mind: Global Pediatric Clinical Trials Network Recommendations and Insights for Sponsors of Pediatric Research [Internet]. DCRI; 2019 [cited 2023 Dec 04]. Available from: https://dcri.org/wp-content/uploads/2019/11/GPTN-whitepaper_07nov2019.pdf
45. Fátima R. Paediatric Medicines: Formulation Considerations. Archives of Pharmacy andPharmaceutical Sciences. 2017;1(1):024-027. Availablefrom: https://www.heighpubs.org/hps/apps-aid1004.php
46. Ivanovska V, Rademaker C, van Dijk L, Mantel-Teeuwisse A. Pediatric Drug Formulations: A Review of Challenges and Progress. PEDIATRICS. 2014;134(2):361-372. Available from: https://pubmed.ncbi.nlm.nih.gov/25022739