Journal of Medicinal and Chemical Sciences 6 (2023) 3057-3071

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

An Overview and Comparison of Regulatory Pathways and Guidelines for Pediatric Study Plans in the US and EU

Chinmayi C S[1], Pratheksha S[1], Lavanya Mude[1], Madhukiran Parvathaneni[2,3,4], Kalaivanan R[5], Veera Venkata Satyanarayana Reddy Karri[1,*]

[1]*Department of Pharmaceutics, JSS College of Pharmacy, JSS Academy of Higher Education & Research, Ooty 643001, India*
[2]*Department of Biotechnology, Harrisburg University of Science & Technology, 326 Market Street, Harrisburg, Pennsylvania, USA 17101*
[3]*Arni Medica, 4475 South Clinton Ave, Suite 230, South Plainfield, NJ 07080, USA*
[4]*CRC Pharma LLC, 333 Littleton Road, Parsippany, NJ 07054, USA*
[5]*Department of Pharmaceutics, PSG College of Pharmacy, Peelamedu, Coimbatore 641004, India*

ARTICLE INFO

Article history

Receive: 2023-07-07
Received in revised: 2023-08-04
Accepted: 2023-08-06
Manuscript ID: JMCS-2307-2151
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatima Ramezani
Editor who approved publication:
Dr. Kiran Chinthapally

DOI:10.26655/JMCHEMSCI.2023.12.21

KEYWORDS

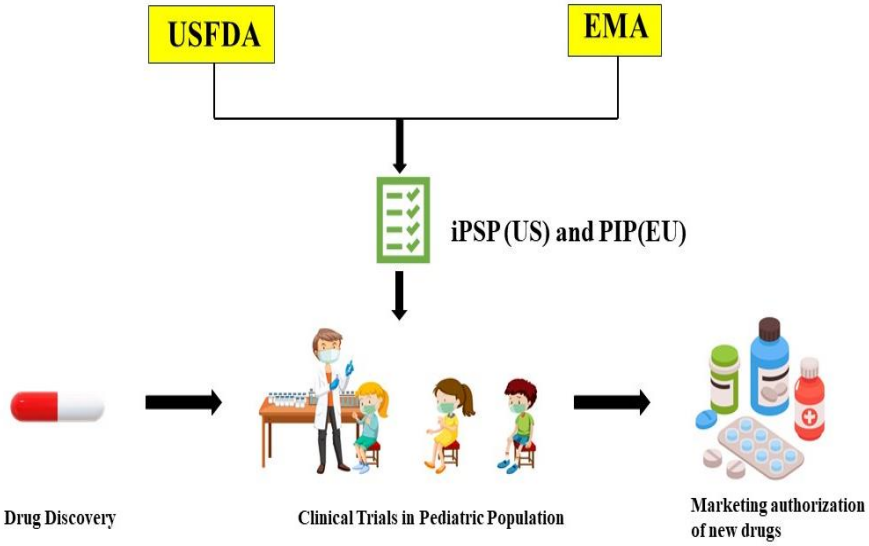
Pediatric studies
US FDA
EU
iPSP
PIP

ABSTRACT

Pediatric research is critical to the development of safe and effective treatments for children. The US Food and Drug Administration (FDA) and the European Union (EU) have produced guidelines to promote and oversee pediatric research. Initial Pediatric Study Plan (iPSP) and Paediatric Investigation Plan (PIP) are regulatory documents aiming to ensure therapeutic product development includes studies in pediatric patients. The US FDA requires an iPSP, in the development of all new medications that are not approved for pediatric use. In the European Union (EU), a PIP is required for all new medicinal products, including those intended for adults, unless a waiver or deferral is granted. An iPSP and PIP are similar documents that outline similar information on the drug's pharmacokinetics, safety, and efficacy in young patients. However, there are minor discrepancies between the two documents' requirements. This article provides an overview of iPSP and PIP requirements and highlights the similarities and differences between the two plans. For instance, the iPSP is only necessary for pharmaceuticals that have not yet been licensed for use, whereas the PIP is required for all new medications. In addition, the PIP includes more detailed information on the proposed studies and timelines for completion. In conclusion, regulatory agencies in both the US and EU have developed guidelines to promote and regulate pediatric studies. While their approaches differ, the overarching goal is to ensure children get safe and effective treatments.

* Corresponding author: Veera Venkata Satyanarayana Reddy Karri
✉ E-mail: Narayana.reddy@jssuni.edu.in

GRAPHICAL ABSTRACT



Introduction

Pediatric patients are a group of patients aged between zero to sixteen years [1]. It is really important to conduct pediatric clinical trials because they help us collect reliable information about how safe and effective medical treatments are for children [2]. They guide clinical decision-making, inform treatment guidelines, and improve care for pediatric patients with unique characteristics that impact their response to medical interventions [2]. Teens, adults, and kids had similar average amounts of warfarin in their blood in a study that looked at the amounts of warfarin, vitamin K1, vitamin K-dependent proteins, and the International Normalized Ratio (INR) in patients who had been on warfarin for an extended period [3]. However, when compared with adults, prepubertal patients had considerably lower plasma concentrations of protein C and prothrombin fragments one and two, as well as greater INR and INR dose1, indicating a better response to warfarin in kids [3]. This finding underscores the need to consider this heightened response when estimating warfarin doses for children and shows the difference in drug response when compared to adults [4]. At a children's hospital and pharmacology laboratory, a study was conducted involving 56 subjects with ages ranging from 3 months to 39 years old [5]. Peripheral blood monocytes were cultured with varying concentrations of cyclosporine, and their proliferation and interleukin-2 expression were measured. The infants (0-1 year old) showed lower IC50 and IC90 values compared to older subjects, while the three older age groups had similar IC50 and Emax values for monocyte proliferation. Lymphocyte subtype proportions were similar across all age groups, and experimental conditions did not affect monocyte proliferation, except for the highest cyclosporine concentration, which reduced monocyte viability. Clearly, age seemed to play a significant role in the *in vitro* pharmacodynamics of ciclosporin. This finding, if overlooked, might pose an unforeseen iatrogenic risk during paediatric immunosuppressive therapy. Understanding these age-related effects could lead to safer and more tailored treatments for young patients [6]. Predicting the harmful effects of drugs in children and infants based on data from adults may not be accurate because how drugs are processed by the body can vary between children and adults [7].

The liver damage caused by sodium valproate is believed to be connected to changes in how the drug is processed in children younger than three years old [8], while the grey baby syndrome, causes cyanosis and cardiorespiratory failure in neonates [9].

Changes in how drugs are processed by the body can sometimes be beneficial, like when young children have an improved ability to break down paracetamol through sulphation. This helps reduce the chances of liver damage if they accidentally take too much of the medication [10].

Regulating pediatric clinical trials aims to ensure ethical and safe research involving children, promote scientific rigour, assess intervention safety and efficacy, enhance transparency and accountability, and facilitate international collaboration [11]. These regulations protect the rights and welfare of pediatric participants, advance pediatric knowledge, and improve child health and well-being [11]. The purpose of this review is to assess the similarities and differences between Pediatric Clinical trials in US and EU and propose harmonization which would support the activities of the Pediatric Cluster in providing better common commentaries [11].

Initial pediatric study plan (iPSP)

The founder of modern pediatrics, physician Abraham Jacobi offered the first medical lecture on the diseases of childhood in 1890. Pediatrics was considered as a part of obstetrics until the Civil War in the United States [12]. In 1994, the United States began improving pediatric information on drug labels through the Food and Drug Administration (FDA) Final Rule. This rule included a section specifically for pediatric use [13]. In simple terms, information from studies involving adults could be used for conditions in children if their disease process and response to treatment are similar to adults [14]. For instance, Erlotinib, a pill that stops the epidermal growth factor receptor tyrosine kinase, can hinder cell cycle progression and potentially shrink tumours. This anticancer medicine has been approved by the FDA to treat cases of adult glioblastoma. After the initial trials in adults, two-phase one studies were conducted with children to examine the safety and how the medication is processed in their bodies at different doses. The design and organisation of the paediatric trials, however, only partially included the insights learned from the adult trials [15].

It is necessary to conduct safety and pharmacological studies in pediatric populations to support its use [16, 17]. Thus, the Food and Drug Administration Modernization Act (FDAMA) came into effect in 1997 because there were no previous techniques and it was considered that a special law would help stimulate the development of pharmaceuticals for children. This law provided incentives to manufacturers who conducted studies on drugs for children, encouraging them to market these drugs [18]. As a result of this law, pediatric researchers have six months of exclusivity in exchange for conducting pediatric studies known as the pediatric exclusivity provision [19]. As described in the FDAMA report, pediatric exclusivity has provided useful information on product labelling and prompted many pediatric studies on drugs [19]. In 1998, the Food and Drug Administration passed the pediatric rule to promote and require studies in pediatric populations. The purpose of this rule is to make sure that new medicines and biological products for children are safe and work well [20]. This then leads to the formation of the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA).

Best pharmaceuticals for children act (BPCA)

The exclusivity incentive was reapproved by the BPCA in 2002 [21, 22]. In exchange for the voluntary completion of paediatric clinical studies described in FDA Written Requests, the BPCA provides sponsors with extra marketing exclusivity [23, 24]. To get a WR, the sponsor should submit a Proposed Paediatric Study Request (PPSR) to the FDA, outlining the indications to be addressed and the studies that would be conducted [23]. If the applicant is eligible for pediatric exclusivity based on the study reports submitted, it depends on the WR [23]. After receiving the WR, submit the study reports [15]. After the FDA has issued a WR,

companies are required to must provide research results populations to the FDA [23]. A WR is a set of documents that explains how clinical trials should be done and what quality they should have. It is not just a protocol [23]. The FDA gives documents to sponsors who want to conduct trials for children [23]. Conducting clinical studies based on written requests is completely voluntary [23].

Pediatric research equity act (PREA)

If specific conditions are met, PREA mandates sponsors to test new products, such as drugs and biological agents, in children, unless the FDA exempts them (grants automatic full waivers) [14]. PREA applies to all new drug applications, no matter what the indication is, the active ingredient used, the form in which it is taken, how it is dosed, or how it is administered [14]. There is a compulsory study requirement, but it is restricted to the approved indications for adults [14]. Any product development program under PREA requires an initial Pediatric Study Plan (iPSP) to be completed [14]. If a biosimilar product has been granted orphan designation, it is exempt from PREA. If not, biosimilar product development programs have to follow PREA regulations [24]. After receiving FDA approval, studies conducted under BPCA or PREA need to undergo a safety evaluation specifically focused on children by the Pediatric Advisory Committee (PAC) within eighteen months [24]. The iPSP was created because of the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA). It is a requirement for drugs and biologics meant to treat or prevent serious diseases in kids. It is significant in the current regulatory landscape as it is required for all sponsors that plan on submitting a new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA) for drugs and biologics intended for the treatment or prevention of serious diseases [14]. The iPSP aims to gather the required data for safely and effectively using the drug in children [25].

Paediatric investigation plan (PIP)

A PIP means generating data to determine the conditions under which a medicinal product can be authorised to be used in paediatrics [26]. Children under eighteen make up the paeditric population [26]. The US pediatric law has been around for a long time, and the EU paediatric law was heavily inspired by it [27]. In 2007, the Pediatric Committee (PDCO) was created at the agency to evaluate and agree on PIPs and waivers [26]. The EU Paediatric Regulation became effective on 26 January 2007 [26]. The main goal of this plan is to make sure there is more information available about how medicines are used for children [26]. To support paediatric research, the Agency launched the European Network of Paediatric Research- European Medical Agency (ENPR-EMA) in 2009, a European network of existing national and European paediatric-research networks and centres [28]. PIP applications are submitted when there is a new active substance or already authorized product [29, 30]. Beginning October 10, 2021, the inclusion of a Research Product Identifier (RPI) number will be mandatory for pediatric procedures and should be incorporated into the electronic application form for PIPs, PIP modifications, and waiver requests [29]. According to post-marketing authorization requirements, the holder must make the drug available for sale with the pediatric indication within two years of the approval date [31].

Legislative obligations and requirements of pediatric study plans

USFDA

All sponsors are required by PREA to perform studies to assess the safety and efficacy of their medications in children [24]. In 2012, they added new rules that made it necessary for all sponsors to include a planned timetable and a planned outline for studies involving children when applying for Investigational New Drug (IND) approval [24]. This proposed plan is known as the iPSP [25]. An IPSP is required by any sponsor that intends to submit a marketing application for a New Drug Application (NDA) or Biological License Application (BLA) [24]. Initial pediatric plan can be submitted for [24]:

(a) A new substance that is effective in treating a condition,
(b) A new use or purpose for a drug,
(c) A new way of taking the medication,
(d) A new schedule for taking the medicine,
(e) A new form or type of dosage, and
(f) Medicines created specifically for children.

The FDA thinks that biosimilar products without the interchangeability designation have new active ingredients. Sponsors have to provide an iPSP for any new PREA submission or supplement, even if the FDA previously granted a waiver or deferral for the same medicine [14].

EMA

The Paediatric Regulation is applicable in the European Union when a new use, form, or way of giving medicine to children is created [27]. The regulation includes obligations for developing medicinal products that have potential use for paediatric patients, and a reward of a six-month patent extension is granted if all measures in the agreed PIP are met. In the EU, there is a single law that combines the incentive and requirement. If you meet the requirements, you have the option to receive either a six-month extension for the Supplementary Protection Certificate (SPC) or a two-year extension for drugs designated as orphan drugs [27, 28]. Paediatric Use Marketing Authorization (PUMA) is a new type of marketing authorization established to encourage the development of permitted items for children that are no longer protected by intellectual property rights. When a PUMA is provided for children, items created specifically and according to a jointly agreed plan (PIP), allow exclusive data access for a period of ten years [27, 28].

Waivers

USFDA

The Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) outline the FDA's requirements for pediatric evaluations and reports, which require drug manufacturers to carry out research in pediatric populations to determine the safety as well as the efficacy of drugs for children. However, the FDA recognizes that there may be circumstances in which pediatric trials are not practicable, appropriate, or necessary, in which case exemptions or waivers may be granted [14].

To request an exemption or waiver from pediatric evaluations and reports, drug manufacturers are required to submit a formal request to the FDA, typically as part of their New Drug Application (NDA) or Supplemental New Drug Application (sNDA). The FDA reviews these requests on a case-by-case basis, considering the specific circumstances and supporting evidence provided. The decision to grant an exemption or waiver is based on the FDA's assessment of the risks and benefits. It is important to note that the FDA's decision to grant exemptions or waivers is based on rigorous evaluation [32].

In certain situations, the FDA can permit drug manufacturers to skip necessary evaluations or reports for children if there are reasons like no pediatric use, ethical issues, logistical difficulties, lack of scientific necessity, or other strong justifications. Waivers are evaluated on a case-by-case basis and are granted when conducting pediatric studies is not feasible, appropriate, or necessary, and when supported by detailed justifications and evidence. The FDA's initial objective is to assure drug safety and efficacy in pediatric populations [33].

EMA

If there is evidence to suggest certain medicines or groups of medicines may not need to provide the information mentioned in Chapter 1- General Authorization Requirements, Article 7(1)(a) [31]:
(a) That the medicinal product(s) may be ineffective or unsafe for some or all children;
(b) The medicine is meant to treat a disease or condition that only adults get, and
(c) The medicine does not help children as much as other treatments do.

Deferrals

USFDA

Sponsors can ask for a delay in reviewing pediatric studies or reports on targeted pediatric cancer treatments after submitting their applications. The FDA does not formally say yes

or no to the request for a delay during a review of the plan for pediatric studies [12]. The formal grant of a delay occurs when the FDA issues an NDA, BLA, or supplemental approval. The iPSP needs to mention any plans to ask for a delay in conducting required PREA studies that are not included in the application (e.g., NDA, BLA, and Performance Supplement) [12]. The sponsor needs to provide an approved plan to the NDA/BLA when applying for a delay in pediatric evaluations or submitting reports on pediatric cancer research with targeted therapies [32]. Hence, it is important that the information provided in this section is comprehensive and regularly kept up to date.

EMA

It is possible to submit a request to delay the initiation or conclusion of some or all of the activities mentioned in the plan [31].
(a) A postponement needs a valid reason based on science, technology, or public health.
(b) If it is necessary to study adults first or studying children will take longer, a postponement can be allowed. (c) The time between the PIP agreement and the start of the paediatric clinical investigations stated in the PIP plan may be prolonged, with applicants having the option of requesting a postponement.

Exclusivity

USFDA

The six-month extension of market exclusivity applies exclusively to the initial period of exclusivity, and a second period would only apply to the specific product [34-36]. The Pediatric Exclusivity Study Age Group represents specific age categories of participants within studies that can be presented as evidence to substantiate claims for pediatric exclusivity (Table 1). In the US, an FDA Board makes its decision on the application, which includes the research indicated in the WR, within ninety days of receiving it [35]. The FDAAA (Food and Drug Administration Amendments Act) became legislation if the original WR was issued before September 27, 2007. If it was given after September 27, 2007, a decision should be made within one hundred eighty days of applying for it [35].

EMA

In the European Union, a single piece of legislation combines the incentive and the requirement for drug development in children [24]. If the requirement is met, a company can get either a six-month extension for their patent SPC or a two-year extension for exclusive rights in the market (for products designated as orphans) [37, 38]. In addition, the PUMA was created to help develop medicines for children, especially for those that are no longer protected by patents [24]. If a product designed for children and following the agreed rules is approved by PUMA, it will have data protection for ten years [24, 38].

Submission process

Submission procedure [12]

1. A sponsor who plans to apply for marketing approval for a new medicine, new dosage form, new active ingredient, or new method of administration should submit an iPSP.
2. Before the investigation deadline, a sponsor should submit an iPSP to PREA, and it should be done within sixty days after the end-of-phase two meetings.
3. If the meetings at the end of phase two do not happen, the sponsor needs to submit the iPSP before starting any phase studies.
4. No matter if the IND covers phase two and phase three studies or not, the sponsor has to submit the iPSP at least two hundred ten days before sending a marketing application.
5. If there are any special circumstances, the sponsor should contact the Centre for drug evaluation and Research or the Centre for biologics evaluation and Research.
6. Once the submission is received, the FDA has ninety days to analyze it and either send a written request or have a meeting with the sponsor to talk about the iPSP.
7. The review process includes talking with the FDA's Internal Pediatric Review Committee.
8. The sponsor receives an additional ninety-day period to go through the FDA's comments.

Table 1: Pediatric exclusivity study age group [21]

Name	Definition	FDA code
Neonates	Newborns up to 1 month	Neo
Infants	1 month old to 2 years old	Inf
Children	2 to 12 years old	Chi
Adolescents	12 to 16 years old	Ado
Other	Other age groups studied	Other

9. The sponsor needs to submit an approved iPSP before the second ninety-day period ends.
10. The FDA has thirty days to evaluate the approved iPSP and make decisions.

EMA

Submission procedure [31]

1. The Agency has to give the applicant the opinion of the Paediatric Committee within ten days of receiving it.
2. Within thirty days of receiving the opinion of the Paediatric Committee, the applicant may submit a written request to the Agency for a reconsideration of the opinion, providing detailed reasons for the request.
3. The Paediatric Committee will appoint a new rapporteur and give a new opinion within thirty days of getting the reconsideration request. This new opinion will either confirm or change their previous opinion. Both the applicant and rapporteur have the option to ask the applicant questions directly. The Paediatric Committee will be promptly notified in writing by the rapporteur of the specifics of any correspondence with the applicant. The updated opinion will be well-supported and come with a justification for the result reached, making it final.
4. The Paediatric Committee's judgement shall be considered final if the applicant does not request reconsideration during the thirty days stated in paragraph 2.
5. After receiving the Paediatric Committee's final recommendation, the Agency will decide within 10 days and inform the applicant in writing of that decision, along with the final recommendation of the Paediatric Committee.
6. If a class waiver is required as described in Article 12, the Agency will decide within ten days of receiving the recommendation of the Paediatric Committee, as described in Article 13(3), and will take that recommendation into account.
7. After any commercially sensitive information has been removed, the Agency's decisions will be made available to the public.

Review and timeline of applications

USFDA

If required by the PREA, the sponsor should submit the iPSP before the deadline for submitting the required studies or evaluations, and it should be done within sixty days after the Phase Two meeting. Alternatively, it can be submitted at a later date as agreed upon by the FDA and the FDA sponsor [14]. The sponsors of investigational new drug applications (IND) can use this resource to learn more about Phase 2A (EOP2A) meetings [14]. The objective of the EOP2A meeting is to promote communication between the FDA and sponsors who are seeking guidance on designing a clinical trial using clinical trial simulation and quantitative modelling of previous knowledge, such as drug and placebo response as well as the disease [39].

General Guidance

Before phase III investigations begin or within sixty days after the Phase II (EOP2) meeting ends [40]. It is not possible to approve an iPSP agreement until two hundred ten calendar days before submitting a marketing application [39].

Biosimilars specific

FDA recommends not less than two hundred ten days before the initiation of a clinical study [39]. Depending on the type of clinical study may be

appropriate to submit iPSP in the earlier stages of development [39].

EMA

The process for submitting and reviewing a Paediatric Investigation Plan (PIP) typically lasts for nine and ten months [40-42]. The process initiates when the applicant submits an ''intent to file'', prompting the Paediatric Committee (PDCO) to appoint a ''rapporteur'' to head the evaluation and a ''peer reviewer'' to verify its quality [41]. The rapporteur and peer reviewer scrutinize the initial PIP and report their discoveries to the PDCO [40].

The evaluation process spans one hundred twenty days, with a brief halt on day sixty for the PDCO to inquire about the applicant [40]. These halts, termed ''clock stops'', normally persist for up to three months, although the duration is negotiated on a case-by-case basis [39]. Once the applicant responds to the PDCO's inquiries, the clock resets on day sixty-one, and the process continues until it concludes on day one hundred twenty without further interruptions [40]. Therefore, all outstanding inquiries must be addressed during this time [40]. If there are still questions that have not been answered after the third interaction with the PDCO, either the PDCO or the applicant can ask for a spoken explanation [40].

Comparison of template between iPSP and PIP

PIP and iPSP typically follow a structured template that outlines the essential components required to ensure the appropriate study of a medicinal product in the pediatric population (Table 2).

Statistics of pediatric study plans

USFDA

Since 2012, there have been reviews of pediatric studies conducted under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). The total number of products studied under BPCA amounts to 51. Under PREA, there have been 428 products studied. Furthermore, 44 products have been studied under both BPCA and PREA during this period [43].

EMA

Between January 1996 and December 2019, approximately 34% of the total medicinal products and 38% of the active substances were specifically intended for pediatric use. Throughout the periods before and after the Paediatric Regulation implementation, the proportion of pediatric medicinal products to the overall medicinal products remained steady, while the proportion of pediatric active substances to the overall active substances decreased. Excluding generics and biosimilars, a total of 106 and 175 pediatric medicines were granted new indications, dosages, or age groups during the two-time frames. Out of these 175 medicines, 128 underwent approval through a Paediatric Investigational Plan, while the remaining 47 were approved without such a plan. These 47 medications were re-purposed from off-patent drugs, following the guidelines specified in Directive 2001/83/EC [44].

Similarities and differences between iPSP and PIP

Similarities between iPSP and PIP

1. Both documents strive to make sure that the creation of medicines for children is done in a way that keeps them safe and healthy.
2. Both documents cover similar areas, including the proposed indication(s) for the medicinal product, the patient population to be studied, the study design, the endpoints to be evaluated, and the safety and efficacy assessments to be conducted.
3. Both iPSP and PIP involve consultation with pediatric experts: Both documents require consultation with pediatric experts to ensure that the development program is appropriate for the pediatric population. The consultation may include paediatricians, clinical pharmacologists, and other experts with experience in the use of medicinal products in children.
4. Both programs have a common goal: To develop pediatric treatments effectively and efficiently worldwide. The labelling of these

treatments reflects the findings of the studies conducted.

5. The PSP and PIP have common scientific elements such as information about the product, details about the disease and treatment, requests for exemptions and delays, plans to create suitable formulations for different age groups, strategies for preclinical and clinical studies, the timing of the studies, and the use of extrapolation.

6. Both programs have 6 months of patent exclusivity.

Novartis' product, imatinib, had a European patent that was given on January 19, 2000. After completing the PIP, Novartis got a 6-month extension for Imatinib's protection in the Netherlands until December 20, 2016.

Table2: Template comparison between iPSP and PIP [14, 42]

iPSP	PIP
Table of contents	Table of contents
1. Overview of the disease/condition in the pediatric population (1-3 pages) 2. Overview of the drug or biological product (1-3 pages) 3. Overview of planned extrapolation to specific pediatric populations (1-3 pages) 4. Planned request for drug-specific waiver(s) (1-3 pages) 5. Planned request for deferral(s) of pediatric studies (1-2 pages) 6. Tabular summary of planned nonclinical and clinical development 7. Age-appropriate formulation development (1-3 pages) 8. Nonclinical studies (1-3 pages) 9. Clinical data to support the design and/or initiation of studies in pediatric patients (1-5 pages) 10. Planned pediatric clinical studies 10.1 Pediatric pharmacokinetic or pharmacokinetic/pharmacodynamic studies (1-10 pages) 10.2 clinical effectiveness and safety studies (1-10 pages) 11. Timeline of the pediatric development plan (1 page) 12. Agreements for pediatric studies with other regulatory authorities (1-3 pages)	Application Summary Table of contents Abbreviations Part B-Overall development of the medicinal product B.1. Discussion on similarities and differences in the condition between populations and pharmacological rationale B.2. Current methods of diagnosis, prevention or treatment in paediatric populations B.3. Significant therapeutic benefit and/or fulfilment of therapeutic needs Part C-Applications for product-specific waivers C.1. Overview of the waiver request C.2. Justification for a product-specific waiver C.2.1. Applications based on a likely lack of safety or efficacy in part or all of the paediatric population C.2.2. Applications based on the disease or condition not occurring in the specified paediatric subset C.2.3. Applications based on lack of significant therapeutic benefit Part D - Proposed paediatric investigation plan D.1. Existing data and overall strategy proposed for the paediatric development D.1.1. Paediatric investigation plan indication D.1.2. Selected paediatric subsets D.1.3. Information on quality and non-clinical and clinical data D.2. Paediatric formulation development D.2.1. General strategy D.2.2. Summary of all planned and/or ongoing, measures in the pharmaceutical development Quality-related studies D.3. Non-clinical studies D.3.1. General strategy D.3.2. Summary of all planned and/or ongoing non-

	clinical studies D.4. Paediatric clinical studies D.4.1. General strategy D.4.2. Paediatric pharmaco-kinetic/pharmaco-dynamic studies D.4.3. Clinical efficacy and safety studies D.4.4. Summary of all planned and/or ongoing clinical studies D.4.5. Details of the ongoing pediatric clinical studies D.5. Other studies D.5.1. Modelling and simulation studies D.5.2. Extrapolation studies Part E-Request for deferrals E.1. Timelines of measures in the paediatric investigation plan Part F-References

Table 3: Differences between pediatric study plans- iPSP and PIP

Criteria	iPSP	PIP
History	1994	2007
Age Group	0-16 Years	0-18 years
Committee	Pediatric Review Committee (PeRC)	Paediatric Committee (PDCO)
Acts/Regulations	Best Pharmaceuticals for Children Act (BPCA), Pediatric Research Equity Act (PREA).	Regulation (EC) No. 1901/2006 Of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC, and Regulation (EC) No. 726/2004
Legislations	Separate legislation BPCA (exclusivity) and PREA (requirements)	Single legislation
Exempted Products	Orphan products	Biosimilar products (Biosimilar Infliximab has been approved by EMA to treat irritable bowel syndrome in the pediatric population)
Legislation Requirements	The novel active component, fresh indication, novel dose format, innovative dosing schedule, and novel mode of administration	New active substances and authorized and patented products
Incentives	Six-month patent exclusivity under BPCA	Six-month supplementary protection certificate (SPC)
Waivers	1. If it is not possible or very difficult to do necessary studies (for example, because there are very few patients). 2. If there is clear proof indicating that the medicine or biological item may not be effective or safe for certain or all children. 3. If a drug or biological product does not provide a significant improvement compared to existing treatments for	1. If a certain medicine or group of medicines might not work well or be safe for children. 2. If the medicine(s) is meant for a health problem that only adults have (or only affects certain groups of children). 3. If the medicine(s) does not provide a meaningful improvement compared to current treatments for children.

	children and is unlikely to be used by many children. 4. Furthermore, if it is impossible to create a suitable drug form for a particular age group of children, a waiver may be issued. This waiver will only apply to the children who require that specific drug form and a reason should be provided for why it is not feasible to develop a form for children.	
Deferrals	1. If the drug or biologic product is being considered for approval for adults before the completion of pediatric studies. 2. If it is necessary to wait for more safety or effectiveness data before conducting pediatric studies. 3. If there is another valid reason to delay, like not having fully developed a pediatric version yet.	1. Based on scientific and technical reasons. 2. For public health concerns. 3. It is advised to conduct studies in adults before starting studies in children. 4. If studies in adults can be completed faster than studies in children, it is better to prioritize adult studies.
Submission Time	End of Phase Two A	End of Phase One
Applications	PSP (PREA)Written request (WR)	Information about administration and the product Information about the disease to be treated and how the product can benefit, with a request for a waiver if needed. Proposed plan for developing the product for pediatric use. Request for a deferral if necessary.

**PSP: Pediatric Study Plans; *EC: European Commission.*

They also received similar extensions in other EU countries for pediatric use [45].

Differences between pediatric study plans- iPSP and PIP

Even though there are similarities between both submissions, there are many differences in their criteria (Table 3).

Ethical issues in pediatric clinical trials

Pediatric clinical trials raise several ethical issues that require careful consideration to ensure the safety and well-being of children enrolled in such studies. Some of the key ethical issues include obtaining informed consent, ensuring the appropriateness of the study design and interventions for the age group, balancing the risks and benefits of participation, protecting vulnerable populations, and ensuring equitable access to trial participation [46, 47].

Role of patients and parents in pediatric drug development

To ensure the safety and well-being of children and youth involved in clinical trials, it is important to take certain precautions. Parents may hesitate to enrol their children in clinical trials due to various factors such as minimizing the number of requests made to them, considering their busy schedules, the availability of medicines outside the trial, and ensuring their comfort and compliance to avoid distress. Previous experiences and negative effects from previous trials also play a significant role in their

decision. Parents mostly want to safeguard their children and improve their overall health [48].

To address the developmental needs of children and youth and ensure their maximum engagement and benefit from clinical trials, models such as iCAN/eYPAGnet and others have been developed to facilitate their participation. These models aim to ensure that children and youth are adequately informed about the clinical trial process and their participation is respectful of their age and developmental stage. By taking these precautions, we can enhance the participation of children and youth in clinical trials while also protecting their well-being [48].

The international collaboration between iPSP and PIP- Pediatric Cluster

The International Collaboration Pediatric Cluster is a joint initiative between the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) aimed at promoting the development of medicines for children. This collaboration was established in 2007 to address the lack of suitable pediatric medicines available for the treatment of children, which had been identified as a major public health concern [49].

The Pediatric Cluster seeks to facilitate cooperation and collaboration between the EMA and FDA in the review and approval of pediatric medicines. The initiative aims to enhance the exchange of information, promote joint decision-making, and align regulatory requirements for pediatric drug development. By working together, the EMA and FDA can leverage their respective expertise, resources, and regulatory frameworks to support the development of safe and effective medicines for children [49].

The Pediatric Cluster works with different teams specialising in developing drugs for children, like studying them in labs, testing them on patients, and monitoring their effects. These groups work to develop joint guidance documents, share data and information, and coordinate regulatory activities. The initiative further provides a forum for stakeholders, including academia, industry, patient groups, and healthcare professionals, to provide input and feedback on pediatric drug development [49].

Since its establishment, the Pediatric Cluster has played a key role in advancing pediatric drug development. It has made it easier to approve many new medicines for children, including ones for rare diseases and conditions, and has also helped create guidelines for developing drugs for children. One notable example of the Pediatric Cluster's success is the development of a new drug for the treatment of cystic fibrosis (CF), a chronic genetic disease that affects multiple organs, including the lungs, pancreas, and liver. The drug, called ivacaftor, was developed by Vertex Pharmaceuticals and approved by the FDA in 2012 for the treatment of CF in patients with a specific genetic mutation [50].

Conclusion

In conclusion, the future of pediatric research holds immense promise as we continue to build upon the strengths of both the US and European approaches. By incentivizing research, prioritizing collaboration, and ensuring ethical considerations, we can create a framework that places pediatric patients and families at the centre of decision-making. The torchbearers for future studies in pediatrics will recognize the similarities and differences between these approaches, and strive to create a well-rounded approach that combines the best elements of both systems. Through this synergistic approach, we can enhance our understanding of how medicines and treatments impact children, ultimately improving pediatric care and advancing the field of pediatrics. As we move forward, let us embrace the opportunities to further improve and innovate in pediatric research, shaping a brighter future for the health and well-being of our youngest patients.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

ORCID

Pratheksha S
https://orcid.org/0009-0006-0050-3806
Mude Lavanya
https://orcid.org/0000-0001-7952-8542
Veera Venkata Satyanarayana Reddy Karri
https://orcid.org/0000-0003-2057-3243

References

[1]. US Food and Drug Administration, Pediatric study plans: content of and process for submitting initial pediatric study plans and amended initial pediatric study plans: guidance for industry. Final Guidance, 2020 [Publisher]
[2]. Joseph P.D., Craig J.C., Caldwell P.H., Clinical trials in children, *British journal of clinical pharmacology*, 2015, **79**:357 [Crossref], [Google Scholar], [Publisher]
[3]. Takahashi H., Ishikawa S., Nomoto S., Nishigaki Y., Ando F., Kashima T., Kimura S., Kanamori M., Echizen H., Developmental changes in pharmacokinetics and pharmacodynamics of warfarin enantiomers in Japanese children, *Clinical Pharmacology & Therapeutics*, 2000, **68**:541 [Crossref], [Google Scholar], [Publisher]
[4]. Stephenson T., How children's responses to drugs differ from adults, *British journal of clinical pharmacology*, 2005, **59**:670 [Crossref], [Google Scholar], [Publisher]
[5]. Marshall J.D., Kearns G.L., Developmental pharmacodynamics of cyclosporine, *Clinical Pharmacology & Therapeutics*, 1999, **66**:66 [Crossref], [Google Scholar], [Publisher]
[6]. Chinthapally K., Blagg B.S., Ashfeld B.L., Syntheses of Symmetrical and Unsymmetrical Lysobisphosphatidic Acid Derivatives, *The Journal of Organic Chemistry*, 2022, **87**:10523 [Crossref], [Google Scholar], [Publisher]
[7]. Choonara I., Gill A., Nunn A., Drug toxicity and surveillance in children, *British journal of clinical pharmacology*, 1996, **42**:407 [Crossref], [Google Scholar], [Publisher]
[8]. Fisher E., Siemes H., Pund R., Wittfoht W., Nau H., Valproate metabolites in serum and urine during antiepileptic therapy in children with infantile spasms: abnormal metabolite pattern associated with reversible hepatotoxicity, *Epilepsia*, 1992, **33**:165 [Crossref], [Google Scholar], [Publisher]
[9]. Weiss C.F., Glazko A.J., Weston J.K., Chloramphenicol in the newborn infant: a physiologic explanation of its toxicity when given in excessive doses, *New England Journal of Medicine*, 1960, **262**:787 [Crossref], [Google Scholar], [Publisher]
[10]. Penna A., Buchanan N., Paracetamol poisoning in children and hepatotoxicity, *British journal of clinical pharmacology*, 1991, **32**:143 [Crossref], [Google Scholar], [Publisher]
[11]. WHO, Clinical trials in Children [Publisher]
[12]. Nursing P. Late-Nineteenth and Early-Twentieth Century Pediatrics, 2022 [Publisher]
[13]. FDA, Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling Guidance for Industry, 2019 [Publisher]
[14]. FDA, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans, 2020 [Publisher]
[15]. Yung W.K.A., Vredenburgh J.J., Cloughesy T.F., Nghiemphu P., Klencke B., Gilbert M.R., Reardon D.A., Prados M.D., Safety and efficacy of erlotinib in first-relapse glioblastoma: a phase II open-label study, *Neuro-oncology*, 2010, **12**:1061 [Crossref], [Google Scholar], [Publisher]
[16]. Karesh A., Pediatric Drug Development: Regulatory Expectations, 2015 [Publisher]
[17]. Turner M.A., Catapano M., Hirschfeld S., Giaquinto C., Paediatric drug development: the impact of evolving regulations, *Advanced drug delivery reviews*, 2014, **73**:2 [Crossref], [Google Scholar], [Publisher]
[18]. FDA, FDA Backgrounder on FDAMA, 2018 [Publisher]
[19]. FDA, Guidance for industry circumstances that constitute delaying, denying, limiting, or refusing a drug or device inspection, 2022 [Publisher]
[20]. Boat T.F., Field M.J., eds., 2012. Safe and effective medicines for children: pediatric studies

conducted under the best pharmaceuticals for children act and the pediatric research equity act, 2012 [Crossref], [Google Scholar], [Publisher]
[21]. FDA, Pediatric Exclusivity Study Age Group, 2014 [Publisher]
[22]. Ward R.M., Benjamin D.K., Davis J.M., Gorman R.L., Kauffman R., Kearns G.L., Murphy M.D., Sherwin C.M., The need for pediatric drug development, *The Journal of pediatrics*, 2018, **192**:13 [Crossref], [Google Scholar], [Publisher]
[23]. FDA, Written Requests Issued, 2023 [Publisher]
[24]. Penkov D., Tomasi P., Eichler I., Murphy D., Yao L.P., 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**:360 [Crossref], [Google Scholar], [Publisher]
[25]. Pharmaceutical Law Group, New FDA guidance details how to submit pediatric study plans, 2020 [Publisher]
[26]. EMA, Guidance on paediatric submissions, 2021 [Publisher]
[27]. EMA, Better medicines for children, 2015 [Publisher]
[28]. Vieira I., Sousa J.J., Vitorino C., Paediatric Medicines–Regulatory Drivers, Restraints, Opportunities and Challenges, *Journal of Pharmaceutical Sciences*, 2021, **110**:1545 [Crossref], [Google Scholar], [Publisher]
[29]. Thomsen M.D.T., Global pediatric drug development, *Current Therapeutic Research*, 2019, **90**:135 [Crossref], [Google Scholar], [Publisher]
[30]. EMA. Paediatric investigation plans: questions and answers Publisher]
[31]. EMA, Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance), 2019 [Publisher]
[32]. Trilogy writing. Writing pediatric study plans (PSPs) – the impact of the revised 2016 FDA draft guidance [Publisher]
[33]. FDA, Guidance for industry (draft) - How to Comply with the Pediatric Research Equity Act, 2005 [Publisher]
[34]. FDA, Retrospective Review of Information submitted and actions, 2023 [Crossref], [Google Scholar], [Publisher]
[35]. RAPS, Legislative issues: Pediatric Research and clinical trials registries and databases, 2007 [Publisher]
[36]. Fda, The Pediatric Exclusivity Provision-Status Report to Congress, 2001 [Crossref], [Google Scholar], [Publisher]
[37]. Bauer P., König F., Adaptive paediatric investigation plans, a small step to improve regulatory decision making in drug development for children? *Pharmaceutical Statistics*, 2016, **15**:384 [Crossref], [Google Scholar], [Publisher]
[38]. Rose K., The challenges of pediatric drug development, *Current Therapeutic Research*, 2019, **90**:128 [Crossref], [Google Scholar], [Publisher]
[39]. RAPS, FDA provides guidance on preparation and submission of pediatric study plans, 2020 [Publisher]
[40]. Karres D., Lesa G., Ligas F., Benchetrit S., Galluzzo S., Van Malderen K., Sterba J., van Dartel M., Renard M., Sisovsky P., Wang S., European regulatory strategy for supporting childhood cancer therapy developments, *European Journal of Cancer*, 2022, **177**:25 [Crossref], [Google Scholar], [Publisher]
[41]. EUPATI. Paediatric medicine: Paediatric Investigation Plan, [Crossref], [Google Scholar], [Publisher]
[42]. EMA, Notification of discontinuation of a paediatric development which is covered by an agreed PIP Decision, 2021 [Publisher]
[43]. FDA, Reviews of Pediatric Studies Conducted under BPCA and PREA from 2012 – present, 2023 [Publisher]
[44]. Toma M., Felisi M., Bonifazi D., Bonifazi F., Giannuzzi V., Reggiardo G., De Wildt S., Ceci A., Paediatric medicines in Europe: the Paediatric Regulation—is it time for reform?, *Frontiers in medicine*, 2021, **8**:54 [Crossref], [Google Scholar], [Publisher]
[45]. Lexology, The Hague Court confirms paediatric extension of SPC for former EU orphan drug imatinib, 2016 [Publisher]

[46]. Dipasquale V., Cucinotta U., Romano C., Biosimilars in pediatric IBD: updated considerations for disease management, Biologics: *Targets and Therapy*, 2022, **2022**:57 [Crossref], [Google Scholar], [Publisher]
[47]. Laventhal N., Tarini B.A., Lantos J., Ethical issues in neonatal and pediatric clinical trials. *Pediatric Clinics*, 2012, **59**:1205 [Crossref], [Google Scholar], [Publisher]
[48]. Tsang V.W., West L., Woods C., Koh C.J., McCune S., Mullin T., Smith S.R., Gaillard S., Claverol J., Nafria B., Preston J., Role of patients and parents in pediatric drug development, *Therapeutic innovation & regulatory science*, 2019, **53**:601 [Crossref], [Google Scholar], [Publisher]
[49]. FDA, International Collaboration / Pediatric Cluster, 2022 [Publisher]
[50]. Investors. Vrtx, FDA Approves KALYDECO® (ivacaftor) as First and Only CFTR Modulator to Treat Eligible Infants with CF as Early as Six Months of Age, 2019 [Publisher]

HOW TO CITE THIS ARTICLE
Chinmayi C S, Pratheksha S, Lavanya Mude, Madhukiran Parvathaneni, Kalaivanan R, Veera Venkata Satyanarayana Reddy Karri. An Overview and Comparison of Regulatory Pathways and Giudelines for Pediatric Study Plans in the US and EU. *J. Med. Chem. Sci*., 2023, 6(12) 3057-3071.
DOI: https://doi.org/10.26655/JMCHEMSCI.2023.12.21
URL: https://www.jmchemsci.com/article_177331.html