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REVIEW ARTICLE

Pediatric drug regulations: A global perspective and the imperative for implementation in India

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Abstract

The pediatric population differs from adults in various ways, including physiological factors, pharmacokinetics, pharmacodynamics, and dosage administration. However, many medications prescribed for children are formulated for adults, necessitating dose adjustments throughout childhood. This underscores the need for pediatric drug formulations and regulations worldwide. This review delves into the intricate landscape of international pediatric drug regulations to elucidate key initiatives, challenges, and advancements shaping this field. Commencing with a historical backdrop, the review outlines the evolution of regulatory frameworks across major regions, including the United States (US), Europe, Japan, and China, while underscoring the imperative for the implementation of pediatric drug regulations in India. These regulations mandate age-appropriate dosing, rigorous clinical trials, and thorough labeling to prevent misuse. They require pediatric-specific studies to understand drug effects and dosages and enforce guidelines for off-label use. Agencies such as the US Food and Drug Administration oversee these regulations, ensuring pediatric drugs meet safety standards before approval. In addition, regulations often include provisions for informed consent and parental involvement in treatment decisions, aiming to protect children from adverse effects while providing effective therapeutic options tailored to their developmental needs. In summary, this review emphasizes the importance of global cooperation and harmonized regulations in advancing pediatric drug research. It highlights recent progress while acknowledging ongoing challenges and opportunities in this critical area.

Keywords: Pediatric drug regulations; Drug development guideline; Clinical trials; Best Pharmaceuticals for Children Act; Pediatric Research Equity Act; Pediatric use marketing authorization; Food and Drug Administration; European Medicines Agency

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1. Introduction

Pediatrics focuses on the physical, social, and mental well-being of individuals from birth through adolescence.[1] The pediatric population is divided into preterm newborn infants (from childbirth to 27 days after the predicted date) and post-term newborns (0 – 27 days old), infants and toddlers (28 days – 23 months old), children (2 – 11 years old), and adolescents (12 – 16 or 18 years old, depending on the region) according to the International Council for Harmonization (ICH) topic E11 (CPMP/ICH/2711/99)

and the ICH E11.[2] Figure 1 illustrates the pediatric age classification along with physiological and biological changes.

It is crucial to establish and specify the necessary instruments for acquiring trustworthy information to ensure the quality, safety, and effectiveness of medications intended for children.[3] Due to a lack of readily accessible and age-appropriate formulations, providing pharmaceuticals to the pediatric population can be challenging.[4-7] Many medications prescribed for children are formulated for adults, necessitating dose adjustments throughout childhood.[8] This may involve physically altering a dosage form to achieve a smaller dose, such as splitting a tablet or diluting an injection.[9] While these practices are common among health-care professionals, there is limited information on the potential risks associated with these manipulations, including time-consuming procedures and uncertain effects on drug stability and effectiveness.[10] Consequently, there is a risk of administering either toxic or ineffective doses to children.[11,12]

Error risk may also increase due to drug manipulation. In pediatric and neonatal treatment, dosage calculation errors are the most common pharmaceutical errors.[13] Economic factors have led to the encouragement of tablet manipulation among adults in several nations. There may be a small distinction in tablet characteristics[14,15] (Tables 1 and 2). Thus, splitting tablets might be more economical than purchasing them in the correct dosages. An efficient survey conducted in this region[6] recognized only one product (including suppositories) that did not have a correlation with tablet splitting.[16]

2. Need for clinical trials on the pediatric population

Clinical trials conducted on pediatric populations are essential for several reasons. Firstly, children have different physiological and metabolic characteristics compared to adults.[17] These differences can greatly impact the safety and effectiveness of medications, making it crucial to study them specifically in pediatric populations.[18] Secondly, certain diseases and conditions may manifest differently or exclusively in children, necessitating the need for targeted research and clinical trials in this population. Thirdly, ethical considerations play a significant role in conducting clinical trials on pediatric populations. Children cannot provide informed consent like adults, so it is essential to have specialized regulations and guidelines in place to protect their rights and ensure their safety during clinical trials. In addition, performing clinical trials in pediatric populations allows health-care providers to gather valuable information on the safety and effectiveness of medications in pediatrics of different age groups.[19] Furthermore, the lack of available child-appropriate dosages and application forms for medications also highlights the need for pediatric clinical trials in India.[20] Figure 2 represents the considerations during the pediatric clinical trial.[62]

By conducting advancements in the regulations of clinical trials, specifically in pediatric populations, we can bridge the knowledge gap and provide evidence-based treatment options for children, ensuring their optimal welfare and health care.[21]

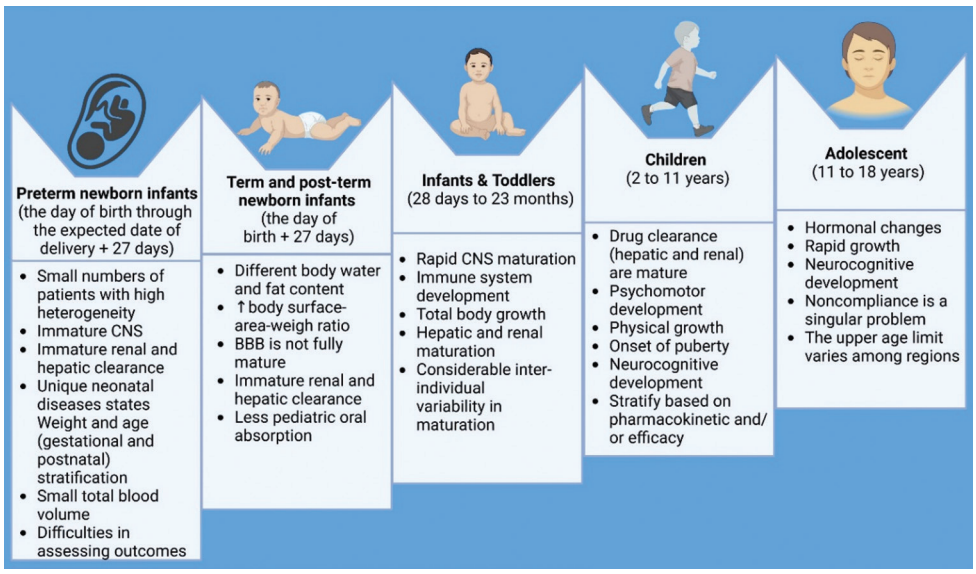


Figure 1. Pediatrics age classification with physiological and biological changes
Abbreviations: BBB: Blood–brain barrier; CNS: Central nervous system.

Table 1. Physiological parameters of pediatrics comparable to the age of adults[14,29,65,66]

Physicochemical specifications	Age at which comparable to adults*
Enteric pH	2 – 3 years
Gastric emptying	8 months
Intestinal colony formation	1 – 4 years
Passive and active transportation in the gastrointestinal tract	4 months
Hepatic circulation	1 year
CYP3A expression in the duodenum	6 – 18 months
Plasma protein levels	1 year
Liver Phase I metabolism	0.5 – 3 years Few attain maturity levels at 10 – 12 years Some changes occur during childhood
Hepatic Phase II metabolism	3 years (Few reach maturity by 10 years)
Glomerular filtration rate	1 – 2 years

Note: *These ages are approximate and may vary according to the literature.

3. The imperative for implementing pediatric drug regulations in India

3.1. Current challenges in pediatric drug development

Guidelines and the acceptance of pediatric drugs are critical aspects of ensuring the safety and effectiveness of medications for pediatrics. Different countries have established their own regulatory frameworks and processes to facilitate the advancement and accessibility of age-appropriate medications for pediatric use.

3.2. Global regulatory frameworks and their impact

One of the main reasons for the absence of age-appropriate versions of original medications and their generic equivalents is due to lower anticipated profits, logistical challenges, and extra developmental work.[22] This can make it challenging for pharmaceutical industries to invest in the development and testing of pediatric drugs.

3.2.1. The pediatric research equity act (PREA) in the United States (US)

For instance, in the US, the PREA was enacted in 2003, requiring pharmaceutical companies to perform pediatric clinical research on new pharmaceutical medicine and biological products before they can be marketed.[18]

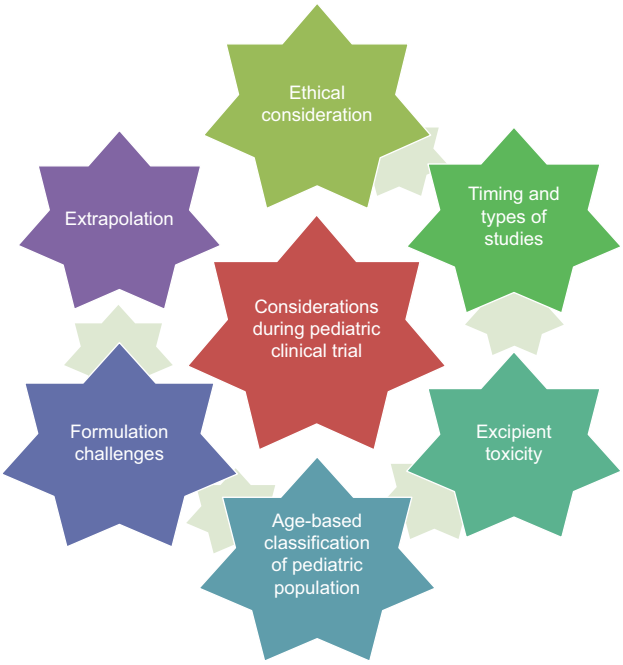


Figure 2. Considerations during pediatric clinical trials[62]

3.2.2. European Union (EU) guidelines on pediatric use

Similarly, in 2007, the EU published the EU guidelines on medicinal formulations for pediatric use, which mandate that pharmaceutical industries submit pediatric investigation plans (PIPs) to the European Medicines Agency (EMA).

These regulations aim to ensure that children can take safe and effective medication that has been specifically tested and approved for their age group. In contrast, the current scenario in India lacks specific drug development regulations for pediatrics. Similar to the EMA's Pediatrics Committee or the US Food and Drug Administration (FDA)'s Office of Pediatric Therapeutics.

3.3. Efforts and recommendations for improvement in India

India currently lacks a distinct department or regulatory structure devoted to pediatric medication development. This lack of specific guidelines for pediatric drug development poses challenges in ensuring the safety and effectiveness of medications for pediatrics. Furthermore, the lack of pediatric-specific guidelines in India has led to irrational drug use and the unavailability of proper dosing information for children.[23] However, it is important to note that there have been recent efforts in India to improve the regulation of pediatric drugs. One such effort is the incorporation of pediatric clinical trials into the regulations for new drug approvals, ensuring that new

Table 2. Problems and remedies in pediatrics clinical trial execution[67-69]

Parameters	Problems	Solutions
Small patient populations	Lack of enrolment increases the chance of unsuccessful study	• Modified research designs • Bayesian architecture • Expert protocol that enables data gathering for various prescription drugs, brands, signs and symptoms, uses, and/or biomarkers • Modeling and simulation techniques to reduce sample size • Careful site selection and use of pediatric research networks • Decentralize, patient-centric approaches to enable wider access
Dosage selecting	Selecting the right dose is essential to increase the probability that the dose under study will have a positive safety and effectiveness profile.	• Pharmacokinetic, pharmacodynamic modeling, and simulation techniques can be utilized to enhance selecting the dosage
Blood volume	Because newborns and babies have small blood volumes, it can be difficult to characterize the pharmacokinetic and pharmacodynamic characteristics of a medication in them.	• When testing blood, think about utilizing ultra-low volume bioanalytical tests and sparse sampling.
Selection of end-points and outcomes	Children should not use adult end-points and outcome measures, which increases the probability of research failure. Caregivers reporting on behalf of children when they are unable to do so on their own	• Make sure the FDA and the key opinion leaders are included early in the study design process to determine • Make sure to utilize validated patient-reported outcomes clinical outcome assessments specifically designed for children • Access reputable online repositories containing approved child-report assessments such as pediatric patient-reported outcomes, common terminology criteria for adverse events, and patient-reported outcomes measurement information system • Make sure target age groups are taken into consideration while designing and testing patient diaries
Adverse event reporting	It can be difficult to get unpleasant incident inf. from pediatrics whose prescription drugs, brands, signs and symptoms, uses, and/or biomarkers are short and their non-verbal interactions with caretakers may be large prevalent	• Apply Ped-PRO-CTCAE to evaluate adverse consequences in kids and teens from 7 to 17 years old, or use it to report caregivers of younger kids
Visits schedule and logistics	Scheduling issues related to schools and families may prevent participation	• Decrease the amount of clinic visits using telemedicine • Take home health and direct patient's medication delivery into consideration • Plan to visit the clinic on the weekends or after work or school
Informed consent	The intricate nature of consent, the impact of cultural aspects and personal experiences, and the lack of regional guidelines	• Using phased informed consent • Using interactive computer technology to explain difficult concepts and changing how to get children's assent depending on multifactorial competence assessments • Individualized instruction for those conducting pediatrics clinical training

drugs are analyzed for safety and effectiveness in pediatrics before they can be marketed. In addition, there have been discussions on the establishment of a separate regulatory body or division within the existing drug regulatory authorities in India to focus specifically on pediatric drugs and their regulation.[24]

These efforts in India aim to address gaps in pediatric drug regulation and ensure that children have access to safe and effective medications. The differences in pediatric drug regulations among India, the US, Europe, and Japan highlight the need for comprehensive and specific guidelines to protect children's health and well-being.

In conclusion, while the US and Europe have made significant progress in pediatric drug regulation by implementing specific laws and regulations, India still lacks comprehensive and specific legislation for pediatric drug development. This regulatory gap poses challenges in ensuring the availability of safe and effective medications for pediatrics in India. However, efforts are being made in India to improve the regulation of pediatric medications, including the inclusion of pediatric clinical research in new drug approval processes.[25] Figure 3 represents the categorization of juvenile age groups.[21]

4. Background: Pediatric drug regulations

Throughout history, there has been a lack of attention given to the development of medications specifically designed for children.[26] In 1968, Shirkey[27] referred to this group as "therapeutic orphans," highlighting their exclusion

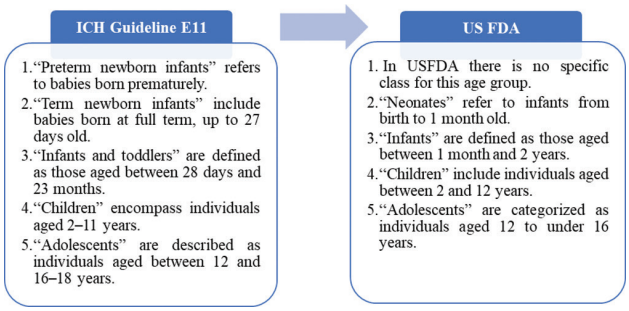


Figure 3. Categorization of juvenile age groups[21]
Abbreviations: ICH: International Council for Harmonization; US FDA: United States Food and Drug Administration.

from research, legislation, and the availability of suitable formulations compared to adults.

The lack of a mandate for studying the efficacy and safety of medicines in pediatrics, considering their particular and distinct qualities, has led to numerous unfortunate incidents over time, some of which have even resulted in fatal consequences.

One of the earliest instances of concern occurred in 1938 when children were administered the antibiotic elixir sulfanilamide. Although adults had previously utilized this antibiotic in the form of pills and capsules, a liquid form was created for pediatric use due to their difficulty swallowing solid dosage forms. To make the antibiotic more palatable, diethylene glycol – a sweet solvent whose safety had not been investigated before – was added to elixir sulfanilamide.[28] Tragically, it later became evident that this substance caused over 100 pediatric deaths. This incident highlights the toxicology implications of excipient safety, which is an essential consideration in pediatric drug development.

In addition, during the 1950s, the thalidomide tragedy – widely recognized for causing irreversible birth defects in over 1000 babies whose mothers used it for its anti-nausea properties during pregnancy – demonstrated the critical importance of pediatric research and the need to ensure drug safety concerning teratogenic effects.[29]

This discussion highlights the serious outcomes of insufficient research on medications for children, particularly among the youngest age groups. Several notable adverse reactions have been linked to commonly prescribed drugs for pediatric use, emphasizing the importance of targeted research in this vulnerable population.

4.1. Sulfisoxazole (Kernictures)

The most significant incident of drug-related harm in children occurred in 1956 when it was discovered that newborns administered sulfisoxazole were experiencing increased cases of kernicterus. This disorder is caused by bilirubin entering the brain, leading to seizures, yellowing of brain tissue, and eventually death. This susceptibility is due to reduced glucuronosyl transferase activity in infants, which reduces their ability to process bilirubin. In addition, the immature blood–brain barrier allows more free bilirubin to reach the brain and cause injury. Since bilirubin is expelled from plasma proteins, a higher proportion remains free in plasma, making it easier for bilirubin to enter the brain.[30]

4.2. Chloramphenicol (Gray baby syndrome)

Gray baby syndrome is an uncommon yet severe adverse reaction observed in infants, particularly premature ones, after receiving chloramphenicol – a bacteriostatic antibiotic – through intravenous administration. This syndrome was initially documented in neonates in 1959. It is believed that the underdeveloped glucuronyl transferase activity and the lack of renal excretion of chloramphenicol and its by-products contribute to the development of the gray baby syndrome.[30]

4.3. Benzyl alcohol

In 1982, benzyl alcohol, a commonly used additive, was linked to neonatal gasping syndrome and preterm infant fatalities. It is utilized as a preservation agent in intravenous line flushes but has been found to cause severe symptoms such as acidosis, respiratory distress, circulatory failure, bleeding in the brain, seizures, and eventually fatalities. This situation serves as a reminder that additives can have significant effects on the body. The issue with the differential metabolism of benzyl alcohol in infants further complicates matters; it is believed that neonates process benzyl alcohol into benzoic acid, which then stores and leads to toxic effects.[19]

Other adverse drug reactions seen in children include liver damage from sodium valproate use,[31] increased risk of Reye's syndrome when using salicylates during viral infections,[32] growth suppression or adrenal function effects from long-term corticosteroid use,[33] gastrointestinal bleeding caused by non-steroidal anti-inflammatory drugs,[34] and arthropathy[35] risk associated with ciprofloxacin use in children resulting in serious consequences.

Adverse reactions such as bronchospasm from antiasthmatic drugs,[19] due to benzalkonium chloride, headaches, and seizures,[36] induced by aspartame, cross-sensitivity reactions in pediatrics with allergies to sulphonamides caused by saccharin-induced compounds, and hyperosmolality and lactic acidosis induced by propylene glycol are among the effects resulting from improper use of excipients in pediatric formulations.[37]

It is reasonable to assume that due to the short availability of pediatric information, children often end up taking medications meant for adult use. This off-label usage is not officially approved according to the product's summary of characteristics.

The global off-label use of pediatric medications exceeded 50% until the late 1990s, especially common in neonatology and intensive care. This trend reduced as children grew older. As a result, it has become crucial to establish regulations and define processes for obtaining accurate information to guarantee the safety, quality, and effectiveness of pediatric medications.

In 2010, the Pediatric Medicines Regulator's Network was established by the WHO in collaboration with Japanese regulators, the FDA, and the EMA to enhance cooperation among regulators through promoting dialog and exchange of information related to regulating pediatric medicines at WHO headquarters in Geneva, Switzerland, on dated February 15 – 17, 2010.

The list of participants in the Pediatric Medicines Regulator's Network is Australia, Azerbaijan, Brazil, Canada, China, Chile, Croatia, Egypt, Europe, Ghana, Indonesia, Malaysia, the Maldives, Moldova, Nigeria, Saudi Arabia, Singapore, Switzerland, Thailand, Ukraine, the United Republic of Tanzania, and the US. In that list of participants, it does not include the name of India because it is not a participant in PMRN.[38]

In contrast to the Pediatrics Regulation and the Best Pharmaceutical for Children Act, there is no benefit to complying with this regulation, leading to the exclusion of orphan drugs. These drugs are intended for rare conditions and are exempt from any obligation, which differs from the earlier pediatrics regulations. Therefore, pediatric research for medications targeting rare diseases (orphans), which are not covered by the PREA, will need to adhere to the Best Pharmaceuticals for Children Act (BPCA) process if they were not originally included in the marketing authorization application (Figure 4).

5. Summary of laws concerning the pediatric population

5.1. EU

In 2007, the pediatric regulation came into effect to make it easier to develop and access medicinal products for children. Its goal is to guarantee that children receive therapies that are duly authorized. Its goal is to guarantee that children receive therapies that are duly authorized and to expand the data on the use of these medications across various pediatric demographics. In the EU, juvenile research has been required for all new products since 2007. This also applies to novel uses, dosage forms, or pharmaceutical versions of products that are already patented or covered by a supplementary protection certification (SPC). Usually, a PIP is necessary unless the EMA grants an exemption based on product-specific reasons or class waiver approval. Compliance with this regulation makes the product eligible for incentives under this legislation's provisions.

5.2. US

In the US, there have been laws and regulations put in place since 1997 to support the development of medical products for children. The existing legislation includes the BPCA, which offers incentives voluntarily, and the PREA, which mandates pediatric development under specific conditions without providing incentives. According to Chapter 5 of the FDA's Safety and Innovation Act, these two regulations were strengthened and enacted in 2012.

5.3. BPCA

Industries financially benefit from the BPCA's enhanced marketing exclusivity, which extends an existing patent or exclusivity for 6 months for the entire product, provided that the sponsor completes the studies outlined in the written request (WR) from the FDA that grants this exclusivity. However, the extensive exclusive period applies only to the specific item being studied. It is important to note that conducting these specified studies is voluntary for sponsors. By submitting a pediatric trial request, they can ask for a WR. Any modifications to a WR can only be made before the sponsor submits the requested studies.

The range of conditions to be evaluated in children is wider than those authorized for use in adults or currently undergoing approval processes. It encompasses all potential benefits of the active ingredient for pediatric patients, regardless of its prior approval status for adults. Therefore, BPCA regulations in the US permit studies for conditions not included in adult indications, which is specifically crucial for uncommon and specific pediatric classifications. The BPCA also offers incentives for orphan categories.

To be eligible for these incentives, sponsors must meet the criteria outlined in the "Guidelines for Industries Qualification for Pediatrics Exclusion Within Section 505A of the Federal Food, Drug, and Cosmetic Act." These guidelines, established in 1999, are presently under revision. For more information about the WR procedure under the BPCA, there are resources available that answer common questions related to pediatric exclusivity. It is noteworthy that the FDA will neither award pediatric exclusion nor issue a WR for studies submitted to them before the issuance of a WR.[39]

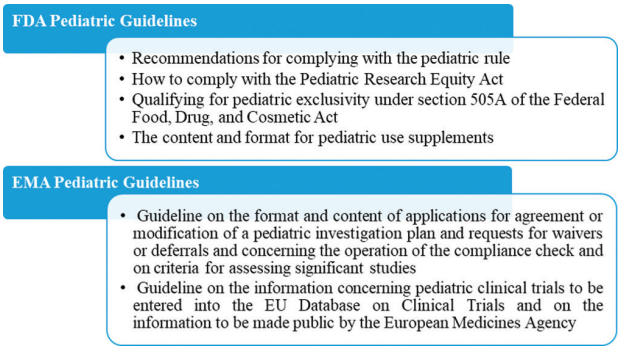


Figure 4. Progress of pediatric drug regulations[64]
Abbreviations: AAP: American Academy of Pediatrics; BPCA: Best Pharmaceuticals for Children Acts; FDA: Food and Drug Administration; FDAMA: Food and Drug Administration Modernization Act; FDASIA: Food and Drug Administration Safety and Innovation Act; FD&C: The Federal Food, Drug, and Cosmetics Act; PAC: Premature Atrial Contraction; PREA: Pediatric Research Equity Act.

5.4. PREA

The PREA mandates that sponsors assess the safeguards and effectiveness of novel items, including pharmaceuticals and biological agents, in youngsters under particular circumstances. However, a waiver from the FDA can be granted. The PREA applies to any product registration for a novel dosage type, novel effective component, novel dosing schedule, novel mode of administration, or novel indications. These studies are compulsory but are confined to the approved indications in adults. The submission of an initial Pediatric Study Plan (iPSP) is mandatory for all product development programs subject to PREA. Product development programs for biosimilars, unless exempted by orphan classification, must comply with PREA regulations.[40]

At the start of the medication development process, the PSP aims to determine critical juvenile research needs and start preparations for these studies. Any marketing proposal covered by PREA should incorporate an agreed-upon preliminary PSP. It is critical to discuss with the FDA if a pediatric developmental project is deemed inappropriate.

The FDA urges sponsors to include all possible juvenile advancement plans in the PSP, even those that fall within BPCA, even though a PSP is only necessary for pharmaceutical advancement projects under PREA. Proposed pediatric study requests (PPSR) may use these strategies as the foundation to get a WR. As a result, a single product might include a WR and a PSP also, enabling both required and optional studies as well as the possibility of BPCA incentives if the product complies with the trials in the WR. It is noteworthy that although exclusivity is granted under the BPCA utilizing an approved WR, as opposed to a PREA, the PSP is ineligible to function as a PPSR. Furthermore, when seeking pediatric exclusivity under PREA requirements, it is essential to obtain an FDA-approved WR before submitting pediatric studies. The FDA will not grant exclusivity until after receiving an approved WR submission, which can occur without requiring sponsor proposals.

Research projects covered by the BPCA or PREA need to have a pediatric-specific security review done by the Pediatric Advisory Committee within 18 months of the FDA approving a label update.[41] Table 3 represents the conventional "standards" for pediatric medication registry.[70]

6. Regulatory mandates and conditions

6.1. Plan for pediatric development

6.1.1. EU

The requirement to consent to a pediatric investigational plan or waiver is relevant in the following situations:

(i) For all new products, regardless of whether they are safeguarded through patent or supplemental protective certificates
(ii) When a petition is filed for a new diagnosis, dosages, or mode of administration for approved drugs protected by a relevant patent or SPC (designed for usage by adult or juvenile classification).

These regulations also cover items that have been granted orphan status inside the EU. The exceptions include biological products that are hybrid, biosimilar, or generic; they also include homeopathic and ayurvedic remedies, as well as those that are approved under the ethical principle of "well-established use."[42]

It is important to remember that fulfilling a responsibility in the EU entails incentives. The particular benefits are attainable in the context of accepting a PIP (and carrying out research). Stated differently, as the EU has a unified legislative framework for both incentives and requirements, adhering to it qualifies one for a biannual patent extension or a 2 years extension of exclusivity on the market (for items designated as orphans). In addition, a brand-new category of marketing permission called pediatric use marketing authorization (PUMA) was created to promote the advancement of approved products for pediatric markets that are currently not covered by intellectual property rights.

Ten years of data exclusivity are awarded to a PUMA for goods created specifically for usage within the juvenile patient following a PIP.[43]

6.2. Exemptions/waivers

6.2.1. EU

The EMA has the power to give an exemption (waiver) that applies to some pediatric subsets, such as age groups, or to

all pediatric subsets, such as full waivers, where a product is subject to the following responsibilities. There are three established legal justifications:

(i) If a certain medication or class of medications is anticipated to be harmful or ineffectual for pediatric patients
(ii) If the ailment for which the medication(s) is prescribed solely affects adults (or only specific pediatric subgroups); and
(iii) If the medication(s) does not provide pediatric patients with appreciable therapeutic advantages over current therapies.

When conducting informative studies is impractical (for instance, in cases of incredibly rare illnesses in children such as arrhythmia) or in situations when clinical trials employing the specific drug are unlikely to significantly improve pediatric patient outcomes, the third legal basis may be utilized to approve exemptions. Certain items or entire classes of medications may be exempt. Any exception can subsequently be changed or revoked if needed in light of breakthroughs in science and medicine. A waiver that is changed or revoked will only become enforceable 3 years following the termination date.

6.2.2. US

The PREA gives the FDA the authority to disregard or omit the need for submitting a juvenile program under certain conditions for specific age ranges. The FDA can grant either whole or half waivers of this requirement upon its initiatives or at an applicant's proposal. If an applicant seeks a waiver, they must furnish written justification and supporting evidence for their request.

The legal basis for such waivers is as follows:

(i) If conducting necessary studies is not feasible or highly impractical (for example, because there are very few participants)
(ii) Should there be strong proof that the medication or biological substance will be harmful or useless for any or all juvenile class

When a medication or biological substance:

(a) does not significantly improve pediatrics' current therapy; and
(b) is not expected to be utilized by a significant number of individuals;

(iii) Furthermore, a waiver may be considered when it is impossible to develop a suitable pediatric formulation for certain age groups. If this situation arises, the waiver will only apply to those specific pediatric age groups requiring that particular formulation, with a detailed explanation outlining why developing such a formulation is unfeasible.

The legal basis shares many similarities but is not entirely identical between both regions. For instance, the EU regulation does not explicitly permit waiving "highly impracticable" studies, as seen in rare or very rare diseases; thus, lacking feasibility criteria within its legislation per se compared to the US standards. Furthermore, unlike the EU system, which does not grant waivers solely based on lack of meaningful therapeutic benefit unless there also is not substantial usage among pediatric patients – contrary to what is applicable in the US regulatory framework.[44]

6.3. Deferrals

The deferral regulations are alike in both areas.

6.3.1. EU

A PIP that has been agreed upon may permit deferrals for part or all of the pediatric investigations and measures. This means that after requesting a marketing license for adults for the same ailment, these studies may begin and/or end.

Deferrals need to have one of the following justifications:

(i) Research involving children will take more time to complete than research involving adults
(ii) Technological and scientific justification
(iii) When adult studies should be conducted before beginning research on the pediatric group; and
(iv) Causes related to general health.

A precise completion deadline for the research must be chosen and agreed upon when a delay is granted. If the anticipated date of the adult marketing approval application is postponed past the designated date of the pediatric study's completion, the juvenile research might be due.

6.3.2. US

While acknowledging the necessity of a pediatric evaluation, a deferral permits the candidate to provide the research findings following the submission of a new drug application (NDA), BLA, or supplemental NDA or BLA. The FDA may decide to postpone any or all of the pediatric trials until a given time after the drug's adult authorization or the biologic's licensing is issued.

The criteria for granting a deferral include:

(i) If the medication or biological item is ready for adult authorization before juvenile research is finished
(ii) If childhood studies must be delayed until more security or efficacy data are gathered; and
(iii) If there is a different acceptable reason for deferring (such as incomplete advancement of juvenile manufacturing).

In both areas, though, economic reasons cannot be used as a reason for postponement.[45]

Table 3. Conventional "standards" for pediatric medication registry[70]

Important subject	Potential response
Standardization of terminologies	• Encourage cooperation across authorities to promote discourse on the Pediatric Development Plan (PDP)
PDP	• Provide recommendations for safety, effectiveness, and efficiency • Provide general guidance on dose formats • Give technical guidance on age ranges, particular illnesses, pediatric medication dosages, and parts of research in underdeveloped nations • Provide guidelines for the PDP's assessment and material • Offer education and development of capacity
Proposal for permission to perform clinical research	• Gather frequently asked questions on conducting clinical studies, with a focus on developing nations; respond to them and offer references to previously published material (such as that from the FDA or EMA) • Create a reference document • Create a useful guide with FAQs and answers
Pharmacovigilance	• Recognition of interested parties and available resources (networks, databases, etc.) • Creation of suitable documentation
Authentication for The commercialization	• Provide guidelines for the assessment of the application dossier's contents • Specify the supporting documentation that should be sent with the marketing authorization application in cases where a different NMRA has previously evaluated the pediatric plan or dataset • Create retraining and capacity-building initiatives for NMRAs
Transparency of the Network's activities	• Utilize the World Health Organization (WHO)'s website to share knowledge, such as national regulatory documents. • Send out the Network Newsletter biannually • Hold network meetings yearly
Advocacy for research on and development	• Track global network activity (e.g., WHO to secure a time slot for the 2010 ICDRA summit) • Reporting network operations (e.g., Ministries of Health) • Determining the National Center of Excellence for pediatric issues

Abbreviations: EMA: European Medicine Agency; FAQ: Frequently Asked Questions; FDA: Food and Drug Administration; ICDRA: International Conference of Drug Regulatory Authorities; NMRA: National Medical Regulatory Authority; WHO: World Health Organization.

6.4. Incentives and rewards

Financial incentives are linked to the right to intellectual property in both the US and the EU. This is implemented in the EU as a 6-month SPC prolongation, which prolongs the patent. In the meantime, the complete product line with an active moiety will have its market protection extended for an additional 6 months in the US.

Regardless of whether new pediatric indications are granted or studies fail to demonstrate efficacy ("negative" studies), companies can obtain these financial incentives in both regions. What matters is that results from these studies are incorporated into product information (labeling). Instead of focusing only on successful studies, the emphasis is on rewarding pediatric development activities. Both areas value "negative" information, which tells us when it is inappropriate to provide medication to a child and requires it to be listed on product labels.[46]

6.4.1. EU

An SPC is required to be eligible for the primary EU benefit; the patent alone is insufficient. As to the ruling of the European Court of Justice, sponsors can still pursue an SPC to receive the pediatric benefit, even in situations when the calculated length of the SPC is either negative or zero.

As opposed to the typical 10-year period provided as part of the orphan reward, designated orphan products in the EU receive a separate payment (whether or not they are covered by a patent), which includes two additional years of market exclusivity, regardless of patent status.

Finally, off-patent items that receive a PUMA in the EU following the completion of a PIP qualify for an additional benefit: extended data protection lasting for several years.

6.4.2. US

The initial term of exclusivity is covered by market security and can be extended for 6 months for the products containing the active component. A second exclusivity period would apply only to the particular product under investigation. In the US, an internal FDA review process is followed. If the submission was issued before September 27, 2007, and contains research defined in the WR, it will be evaluated within 90 days. For applications submitted beyond this date, a decision must be made within 180 days of receipt.

(i) In the US, pediatric exclusivity is obtained through a different legislative framework than the obligation, as PREA and BPCA are two distinct laws with separate legal foundations and procedures. This distinction may lead to different requirements for pediatric research. However, in the EU, since the specifications and rewards are covered by the same laws and regulations, no further research is required to ensure exclusivity

(ii) The EU and the US have different legislative frameworks. While "condition" is broadly construed in EU legislation according to their policy on determining condition(s) for a pediatric research plan/waiver (pediatric research plan/waiver scope), the US statute limits the requirement to adult indications. The BPCA exclusivity procedure must be used for some pediatric disorders that do not arise in adults

(iii) The primary benefit is associated with the SPC/patent in the EU, while it pertains to security for patents and exclusivity as outlined in the US Orange Book for every medication item that includes the investigated active component

(iv) In the EU, products approved centrally can be promoted across every country of markets, but SPC/patents are granted by every member country, potentially resulting in variations or absence of SPCs across different member countries. Meanwhile, in the US, a medication authorized by the FDA can be marketed nationwide

(v) The incentive in the US applies solely to the optional BPCA-written application regulatory procedure. When research is required due to PREA obligations (e.g., under a PSP), there is no cash reward. However, if a medication falls under both a PSP and WR and consequently has both required and discretionary studies included, there is potential eligibility for incentives if required conditions are met

(vi) Incentives in the US are limited to the optional BPCA-written application regulatory procedure. There is no financial incentive when research is required as part of PREA responsibilities (such as under a PSP). However, if a product is covered by both a PSP and WR As a result, both necessary and elective studies are incorporated; if prerequisites are satisfied, there may be an opportunity for incentives

(vii) For any medications containing the active moiety, a further 6 months of pediatric exclusion is permissible in the US but impermissible in the EU. It is noteworthy that in the US, pediatric exclusivity is only applicable for the first 6 months for all medicines containing the active moiety. Only the product under study is eligible for the second exclusivity period, which is awarded if a pediatric indication is provided

(viii) About orphan products: Orphan products are likewise subject to pediatric exclusion in the US, unlike in Europe, where there are distinct rewards (as previously indicated). In addition, it prolongs the current patent and marketing durations as well as orphan exclusivity and Hatch Waxman Act protection, which are designed to shield novel pharmaceutical goods from competition from generic versions (Figures 5 and 6).

In contrast, sponsors of research involved in a PIP agreement in the EU are granted a 10-year data protection period under the PUMA.[47]

7. Guidelines and procedural advice for PIP, PSP, and WR submission, evaluation, and modification procedures and timelines

7.1. EU

The European Commission Guidelines on the layout and substance of PIP and waiver submissions are the primary regulation accessible in the EU for producers of medical goods concerning pediatric legislation. It was most recently amended in 2014. Additional procedural guidance can be found on the EMA website.

To streamline overall development and integrate the pediatrics program into the adult program, early discussion of it is essential. Obtaining a PIP before requesting clinical trial permission for pediatric research is strongly advised. Within the EU, clinical trials are not EMA, but the appropriate participating country's jurisdiction or states where the trial would take place are in charge of granting authorization. A member state does not need to validate an earlier PIP agreement to obtain authorization. Nevertheless, requesting a retrospective PIP after receiving authorization could not ensure the Pediatric Committee (PDCO)'s consent and might result in further requirements that waste time and resources.[48]

PIP applications are submitted by sponsors to the EMA for assessment by the PDCO. The commission is in charge of evaluating PIPs from a scientific standpoint and reaching a consensus. Under these plans, sponsors may be permitted to implement all or certain PIP measures following their application for marketing permission for adults, with the option for deferrals. The EMA will decide on the approved PIP (or complete waiver) within 10 days of obtaining the PDCO's final opinion. Excluding any clock-stop periods — that is, the time applicants take to reply to PCDO requests – the EMA has a maximum of 7 months to decide on a PIP. In actuality, the full process often takes a year because the average interval is roughly 135 days long.[49]

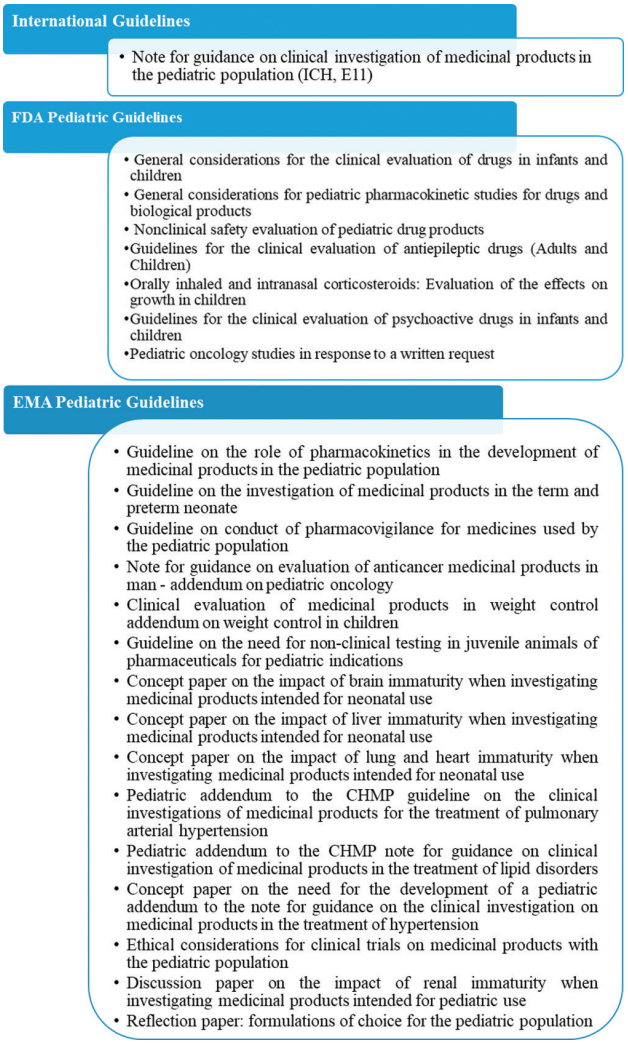


Figure 5. Guidelines for the development and study of pediatric medications[63] Abbreviations: EMA: European Medical Agency; FDA: Food and Drug Administration.

7.2. US

This information on the advancement of medications for pediatrics can be found on the FDA website under "Pediatric Product Development."

7.2.1. Pediatric study plans

Furthermore, by consulting the preliminary guideline paper entitled "Content of and Procedure for Submitting iPSP and Amended iPSP," sponsors can receive assistance in accomplishing the initial PSP applications. A preliminary PSP template that is similar to the PIP application template is also included in this document.

7.2.2. WR

A frequently asked question (FAQ) concerning the pediatric exclusivity process is accessible to offer details on the BPCA-WR procedure, and there is also availability for a 1999 advisory document that is currently undergoing revision.

Based on an individual initiative or a request from a stakeholder, the FDA can issue a WR. To accelerate the FDA's issuing of a WR, sponsors are strongly advised to submit a PPSR to ensure pediatric exclusivity. Sponsors are advised to refer to the "Guidelines for Industries Qualifying for Pediatric Exclusion within Section 505A of the Federal Food, Drug, and Cosmetic Act" for guidance on what should be included in the PPSR. We are at the moment revising this policy document. Sponsors must make sure that their PPSR is submitted with adequate time (about 120 days) for both FDA review and Pediatric Review Committee discussion.[50]

7.2.3. Variations in documentation submission

When comparing PIP and PSP, the section titles in the PSP template closely resemble those of the EU PIP model for intellectual documents (parts B to E), even appearing in the same order.

The FDA generally requires less detailed background information on aspects such as a product's characteristics and its development in adults, as their technical review divisions handle all studies and data related to both mature and juvenile patient development from the opening of an investigational NDA by the sponsor. Conversely, when sponsors reach out to EMA with a PIP application in the EU, they may need to provide more detailed information since it is often their first interaction with them.

Despite this difference, both regions expect concise, stand-alone applications: In the EU, it is suggested that each scientific document for a PIP application should not exceed 40 pages per condition, whereas PSP applications submitted within the US should include between 12 and 60 pages.[51]

7.3. The initial submission of relationships with regulations

7.3.1. EU

EMA has been providing free early pediatric interaction sessions with sponsors since June 2015 to encourage timely conversations about pediatric advancement and the timing and substance of PIP submission. Before submitting a PIP, this new initiative seeks to enable discussion regarding addressing pediatric necessities relating to a particular product. In addition, to guarantee a quick validation procedure at the time of application, a professional initial submission discussion can be set up several months before applying for a PIP or waiver. The PIP/waiver application questions and answers offer guidance.



Figure 6. Scientific guidelines for the development of pediatric medications
Abbreviations: CHMP: Committee for Medicinal Products for Human Use; EMA: European Medical Agency; FDA: Food and Drug Administration.

7.3.2. US

When it comes to juvenile advancement, the FDA is in favor of early participation and conversations. These can start as early as the pre-investigated new drug (IND) phase or at the finish of phase I discussions. This is particularly valid for medications intended to treat life-threatening or fatal diseases. Before the initial PSP filing, these exchanges should occur for advancement programs covered by PREA. Sponsors of advancement programs covered by the BPCA can file a PPSR at any stage of the legislative advancement procedure. WRs can be issued by the FDA at any point during the product developmental process as long as there is enough evidence. There are no costs

associated with filing a PPSR; however, sponsors who wish to complete WR as a component of a marketing proposal or supplementary application must supply the studies and pay any associated fees.

7.4. When should the PIP, PSP, and PPSR be submitted?

7.4.1. EU

A PIP proposal has to be filed early in the medication advancement procedure in the EU, usually after completing pharmacokinetic trials in adult individuals. The EMA accepts the sponsor's ambiguity and specifies that submissions must coincide with the conclusion of pharmacokinetic study and preliminary tolerance research for healthy subjects or patients, or with the beginning of adult Phase II research (proof-of-concept), but not before Phase III studies.

7.4.2. US

Under PREA, the sponsor is required to submit the first PSP within 2 months following the conclusion of the phase II discussion in the US. The sponsor should submit the first PSP as soon as possible, but before starting any phase III investigations or combining phase II and III research, if there is not an end-of-phase (EOP2) conference. The sponsor must submit the first PSP application at least 7 months before submitting a marketing application or supplementary if no phase III or combination phase II and III studies will be completed. It is strongly advised to send an initial PSP before the EOP2 meeting for serious or fatal disorders with limited pediatric treatment options. This will enable product discussions during the initial IND stage or during the EOP2 meeting.[52]

7.5. Method of assessment

7.5.1. EU

In the EU, the method of assessment for PIP involves a thorough evaluation and expert advice from the Pediatric Commission of the EMA. The final decision is made by the EMA. The EMA reviews and validates proposed PIPs within 30 days and then provides a review analysis to the PDCO. After receiving a valid proposal, which is delivered by EMA to sponsors within 10 days of adoption, the PDPC has 60 or 120 days to adopt its opinion. If there is no request for reexamination from sponsors within 30 days, the advice becomes final and results in an EMA conclusion on PIP issuance within a further 10 days.

The maximum review time that an evaluator agency can take includes:

(i) A validation stage of up to 30 days
(ii) A specific timeframe for the EMA to review a PIP:
   (a) Validation: up to 1 month
   (b) Evaluation phase: 1 + 1 month
   (c) Conclusion phase: 40 days (which can be shortened to 10 days upon the application).

This creates a total of 190 days. However, during the time between the first and second (obligatory) evaluation phases, the sponsor has an infinite amount of time to reply to the inquiries from the PDCO for modifications (referred to as the clock-stop period). Although the EMA suggests a response time of 90 days, in practice, it typically lasts about 4.5 months.

7.5.2. US

Under the US PSP evaluation guidelines, the first PSP must be examined within 75 days after receipt, according to Pediatric Epilepsy Research Consortium regulation. Within 90 days of receiving the PSP, the FDA must hold a meeting or provide the sponsor with a written answer. After the meeting with the FDA, the sponsor has 90 calendar days to submit an agreed initial PSP or to receive written comments from the FDA. The FDA provides written confirmation of its agreement within 30 days after the agreed initial PSP submission.

The review period for a PSP in the US would normally last 7 months, and the sponsor could begin the process as soon as 60 days following the EOP2 conference, according to the previously outlined protocol. Initiation should happen before beginning a phase III trial or a combined phase II and III trial (i.e., sooner) if an EOP2 conference is not held. If not, initiation must take place up to 210 days before marketing application submission.

Regarding WRs in the US, the FDA may not respond to the sponsor with a suitable answer for up to 120 days following the submission of the PPSR.

8. Pediatric drug regulations in China

The Drug Administration Law, which became effective on December 01, 2019,[53] clearly outlines the nation's responsibility to promote and prioritize the creation of new forms, dosages, and precise information of pediatric medications that align with children's physiological characteristics. Regulatory agencies are in the process of establishing guidelines, enhancing communication and technical support, as well as securing high-quality resources for clinical trials related to pediatric drugs.[54] The regulatory documents issued in China are represented in Table 4**.** We have received a comprehensive list of all oppositional defiant disorders from 2000 up to December 2012 from EMA. This includes designation dates and numbers, indications, and age categories indicating whether they are intended for use in children or adults (i.e., potential pediatric usage or

not).[55] Figure 7 represents the schedule of modifications to regulations for the advancement of pediatric medications.

9. Pediatric drug regulations in Japan

Since there are no legal requirements for the production of pediatric medication in Japan, the Ministry of Health, Labor and Welfare (MHLW) has implemented a range of initiatives since 2000 to encourage its advancement.[56]

On December 22, 2014, the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (issued by the Ministry of Education, Culture, Sports, Science and Technology and MHLW) were established by merging two existing government guidelines: "Ethical Guidelines for Epidemiologic Research" and "Ethical Guidelines for Clinical Research." These new ethical guidelines marked the first instance of incorporating regulations on "obtaining assent," a procedure particularly relevant to children. This development indicates that Japan is taking initial steps toward addressing issues related to children.

New and distinct pathways for regulation, such as the "high-need medical devices," "system for designating orphan medical devices," the "Sakigake strategy,"[57] "fast-break scheme for innovative medical devices," and "clinical evaluation report system" were introduced to assist the advancement of orphan medical devices in Japan. A significant obstacle in obtaining approval for medical devices targeting rare diseases is meeting clinical evaluation requirements. As alternatives to the traditional submission procedure needing clinical study data, novel approval routes such as the "fast-break scheme" and the "clinical assessment reporting system" have been put into place.[58]

The FDA recently published three guidelines to encourage the initial advancement of medical devices for pediatrics.[58] These include the 2014 Guidance on Pre-market Assessment of Pediatric Medical Devices, the 2014 Guidance on Providing Information about Pediatric Uses of Medical Devices, and the 2016 Guidelines for Using Clinical Data Already Available to Extrapolate to Pediatric Medical Device Usage. Together with these initiatives centered on pediatrics, other programs, such as the Breakthrough Device Program, have been initiated by the FDA to encourage innovation in medical devices. Furthermore, regulatory authorities such as PMDA in Japan have also supported using registry data to enhance evaluation processes for pediatric medical devices while reducing costs and enhancing efficiency.[59]

In addition, three distinctive Japanese projects that are expected to greatly improve the development of pediatric medical devices were found through a search on the PMDA webpage in December 2019: "Conditional Early Approval System for Innovative Medical Device Products," "PMDA Science Board on Evaluation of Medical Devices in Pediatric Use," and "Subsidization Program for Application of Pediatric Medical Device." Each initiative's goals and achievements were examined using data that were made public by the MHLW and the PMDA. The Japan Federation for Development of Medical Devices website was another source of information regarding the Orphan Medical Equipment Registration System that was examined.[60]

Table 4. Regulatory documents issued in China[71]

Guidelines	Regulations	Important considerations
"Guideline 2014"	"Guideline on Pharmacokinetic Studies in Pediatric Population"	(i) Pharmacokinetics in the pediatric population: Study design, methodology, and regulatory considering
"Guideline 2016"	"Guideline on Clinical Trials in the Pediatric Population"	(i) Monitoring and ensuring the safety of data categorizing patients by age (ii) Commencement duration for drug administration (iii) Testing drugs in clinical trials involving children (iv) Planning clinical trials for pediatric patients (v) Choosing suitable dosage forms for children (vi) Conducting clinical trials for rare diseases in the pediatric population (vii) Ethical factors to consider
"Guideline 2017"	"Guideline on Extrapolation from Adults to Pediatric Patients"	(i) Idea of extending beyond known data (ii) Process of predicting based on existing information (iii) Modeling and simulation (iv) Fundamental principles and necessary conditions
"Guideline 2020"	"Guideline on the Use of Real-World Research to Support Development and Regulatory Evaluation for Pediatric Drugs"	(i) Distinctions and suitable integration of experimental in relation to conventional randomized controlled clinical studies (ii) Typical circumstances for the application of practical studies in China's medicine discovery for children

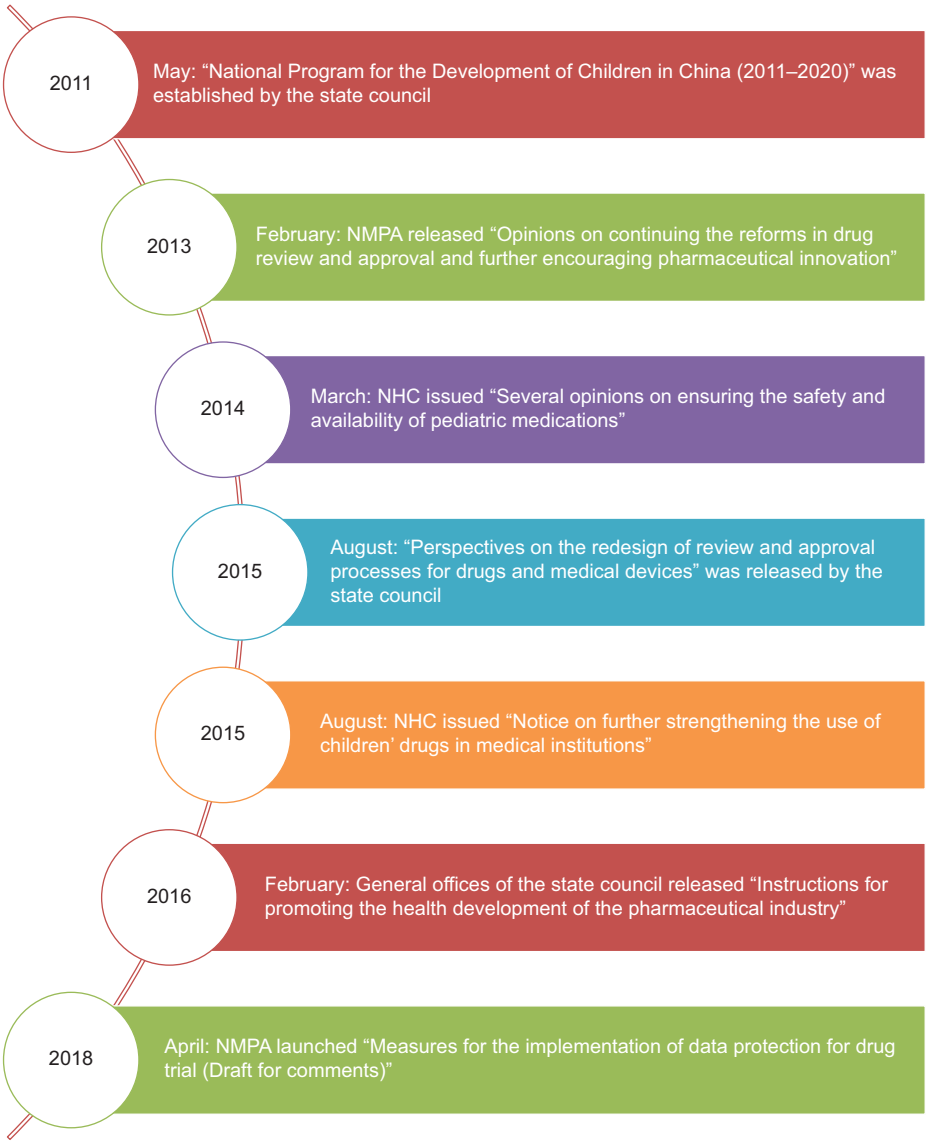


Figure 7. Schedule of modifications to regulations for the advancement of pediatric medications
Abbreviations: NHC: Neonatal Head Circumference; NMPA: National Medical Product Administration.

The Clinical Trials Act, established in 2017 and effective from 2018, along with the Ethical Principles for Medical and Health Studies Including Participants, regulates clinical studies. In addition, the Pharmaceutical Affairs Law and Good Clinical Practice standards govern these clinical studies. Following revisions to the Pharmaceutical Affairs Law in 2002, it became possible for doctors and dentists to act as principal investigators for investigator-initiated trials (IITs). Instead of the sponsor-initiated trials (SITs) that firms normally perform, these IITs arise when industries refuse to sponsor studies for novel uses of pharmaceuticals or medical devices.[61] The duties of SITs and IITs are reported in Table 5.

10. Conclusion

Regulations governing pediatric drug development in India represent a critical step toward ensuring the safety and efficacy of medications for children. The establishment of specific guidelines and requirements by regulatory authorities such as the Central Drugs Standard Control Organization has helped streamline the process of pediatric drug approval and promote the development of age-appropriate formulations. However, despite these advancements, several challenges persist, including the limited availability of pediatric clinical trial data, ethical considerations in conducting research involving children,

Table 5. In performing clinical studies, the duties of sponsor-initiated clinical trials (SITs) and investigator-initiated trials (IITs)

Responsibilities	IITs	SITs
Responsibility holder	Principal investigators conduct their own clinical studies	Pharma Industries
IB, protocol, and SOP before clinical studies	Principal investigators conduct their own clinical studies	Pharma Industries
Production or importation of IP	IP Supplier (Pharma Industries)	Pharma Industries
Clinical study center	Hospital	Hospital
When conducting clinical studies reaction to the regulatory agency throughout as well as after studies (notice of clinical trials submitted, safety reports)	Principal investigators conduct their own clinical studies	Pharma Industries
Monitoring/audit	Principal investigators conduct their own clinical studies (or the individual to whom they allocate)	Pharma Industries
Records (data management, statistical analysis, CSR)	Principal investigators conduct their own clinical studies	Pharma Industries
NDA	Pharma Industries	Pharma Industries

Abbreviations: CSR: Corporate social responsibility; IB: Investigator's brochure; IP: Investigational product; NDA: New drug application; SOP: Standard operating procedure; SIT: Sponsor-initiated clinical trial; IIT: Investigator-initiated trial.

and the need for greater collaboration between regulatory agencies, health-care providers, and pharmaceutical companies. However, we have covered a comparison between countries such as the US, EU, Japan, and China and the need for pediatrics regulations in India.

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Conflict of interest

The authors declare they have no competing interests.

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Availability of data

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