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Pediatric Drug Development Process: A Review

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This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

This review includes New Formulation approaches to improve Pediatric compliance such as Mini tablets, 3D printing, Orodispersible films, Chewable tablets. Various strategies to improve patient adherence such as 'nipple shield' delivery system, dry solid formulations to be converted to liquid at the point of administration, pill swallowing cups, Medicated dosing straw. It is important to formulate pediatric medicines that are tailored to a child's age, size, physiological condition, and treatment requirements. Legislations for pediatric formulation to ensure that products to treat pediatric patients are appropriately authorized for use in the pediatric population, minimize the worst effect of Off-label medication and to improve the information available on the use of these products in the various pediatric populations. Also, the review consists of Information on legislative obligation and requirement, current State, challenges and effect of regulations. Recent progress has been made in the development of pediatric formulations due to new regulations, additional funding opportunities, and collaborative research initiatives.

Keywords: Patient compliance strategies; innovative solutions; pediatric legislation.

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1. INTRODUCTION

Pediatric population oral dosage forms are greatly accepted despite of other dosage forms. Children often face difficulty taking the same dosage forms that are intended for adults. For instance, tablets that allow for adult doses may need to be divided before administering them to younger children [1].

“The use of manipulation and compounding has become widespread because conventional formulations are not intended for Pediatric patient population” [2]. Formulation design focused on the patient that is targeted on overcoming compromised physiological, visual, cognitive, and swallowing abilities [3].

“Due to the wide range of pharmaceutical and clinical factors that must be taken into account in order to assure the quality, safety, and effectiveness of the finished product, developing an age-appropriate formulation is a challenging feat. Pharmacokinetic and pharmacodynamic responses in children are different from those in adults, primarily due to variations in body water and serum protein composition. Additionally, children may experience illnesses specific to their age group, which require medications not available for adults. Unfortunately, most drugs used in children have not been adequately studied in this population, and safety and tolerability data from adult studies are extrapolated to pediatric patients” [4].

“In addition to all the factors mentioned above the manufacturing process of pharmaceutical products must be robust and able to deliver medicines of adequate quality at an affordable price” [5].

“Many available formulations are not suitable for children, leading to off-label and unlicensed use of adult medications. However, recent progress has been made in the development of pediatric formulations due to new regulations, additional funding opportunities, and collaborative research initiatives. These advances include a shift toward oral solid formulations and a focus on novel preparations such as flexible, dispersible, and multi-particulate oral solid dosage forms. These developments have enabled greater dose flexibility, easier administration, and better acceptance of drug formulations in children” [6].

In the interest of meeting the requirements of patients, caretakers, manufacturers, and healthcare practitioners, an ideal formulation must meet a number of criteria. Three categories have been used to group the various factors that must be taken into account when creating age-appropriate products: Patients' access to medications is influenced by a number of factors, including those that are connected to patient safety, efficacy, and convenience of use [7].

To ensure effective treatment for all children, different routes of administration, dosage forms, and strengths may be necessary. A greater emphasis has been placed in recent years on the creation of advance technologies for the development of formulations that are age-appropriate, with changes to the regulatory environment supporting this.

2. NEW APPROACHES FOR PEDIATRIC CENTRIC FORMULATIONS

2.1 Mini-Tablets

The European medical agency (EMA) pediatric guideline suggests that small tablets, also known as mini-tablets, can enhance dosing flexibility and acceptability in children [8]. “However, there is currently no clear definition of what constitutes a small tablet, although a proposed limit of 5 mm is under consideration for public feedback. The guideline emphasizes that the suitability of small tablets should be determined based on the child's health condition, disease progression, and the potential risks of swallowing, choking, aspiration, over-dosing, and under-dosing. Research has shown that 4-mm uncoated mini-tablets are appropriate for children from 1 year of age, while smaller 2-mm mini-tablets can be used in infants as young as 6 months old. Furthermore, 2-mm rapidly dissolving mini-tablets may even be suitable for pre-term infants” [9]. Mini-tablets have been found to be as well accepted or even better accepted than oral syrups in some studies.

“Mini-tablets can offer a versatile dosage form, as even children as young as 2 years old have been able to take 5 to 10 tablets presented in a fruity jelly on a spoon” [10]. “Nevertheless, there are concerns about administering medications concurrently with food or drink since it can affect physical parameters such as particle size, tablet coating, and the release of the active substance, ultimately influencing the bioavailability of the drug product” [11].

2.2 Orodispersible Films

Orally disintegrating films (ODFs) incorporating drugs in polymeric matrices can be formulated to rapidly disintegrate in the mouth, thus releasing the active ingredient. Similar to their predecessor orally disintegrating tablets (ODTs), ODFs facilitate swallowing without requiring water for administration. Additionally, some patients may prefer ODFs due to their elegant appearance. Another advantage of films over tablets is their versatility in dosing, as different strengths can be obtained by cutting films to the desired size [12].

Orodispersible films are thin sheets of polymer, either single- or multi-layered, that dissolve rapidly in the mouth before swallowing. While not explicitly mentioned in the EMA pediatric guideline, the scientific literature increasingly discusses their appropriateness for pediatric drug therapy [13]. The main advantages of these films are their ease of administration, ability to measure dosage accurately, limited risk of spilling, absence of choking hazards, and the ability to cut them into different sizes for dosing flexibility during product manufacturing. However, factors such as patient acceptance, product strength, packaging, and the risk of medication errors associated with the use of this dosage form require special attention.

Fig. 1. Mini tablets

"Polymeric matrix-based ODFs are films containing drugs that dissolve quickly in the mouth, releasing the active ingredient and facilitating swallowing without requiring water. They possess an attractive appearance and may be preferred by some patients. Additionally, ODFs have the added advantage over tablets of being able to achieve different strengths by cutting the films into the desired size" [14].

Eman Dahmash et al. developed 25 mg topiramate-containing oral dissolving films as a suitable substitute dose form for the management of paediatric epileptic diseases. Hydroxypropyl methyl cellulose (HPMC) served as a hydrophilic film-forming agent while glycerin served as a plasticizer in the optimized films. The created film retained the drug's physicochemical stability as determined by TGA, XRD, and SEM analysis while releasing 98% of topiramate within 10 minutes [15].

Konstantina Chachlioutaki *et al.* aimed to "develop Orodispersible films (ODFs) for isoniazid administration to children exposed to tuberculosis. Orodispersible films were created as a kid-friendly dose form to make it easier for juvenile TB patients receiving long-term isoniazid preventative therapy to take their medications orally. Using electrospinning, the ODFs were created from aqueous solutions of natural and semi-synthetic polymer mixtures. Physical and chemical characteristics of the spinning solutions and the produced fibres were obtained".

In contact with artificial salivary juice, the ODFs quickly dissolved in less than 15 seconds, achieving rapid and total ISO release in less than 60 seconds. The findings show that every manufactured ODF formulation is an age-appropriate dose form for children [16].

"Thin films can be easily applied by themselves, especially for dysphagia patients, geriatric, pediatric, or bedridden patients, as well as patients who cannot easily access water. These drug delivery systems can be administered in various ways such as oral, buccal, sublingual, ocular, and transdermal" [2].

2.3 3D Printing

Recent advances in 3D printing technology have created new possibilities for the manufacture of drugs and medical equipment.

"The technology mentioned above focuses on cutting-edge methods for designing solid dosage forms for personalised therapy, transdermal medication, and biomedical applications of additive manufacturing techniques, including implants, surgical models, bioprinted materials, and biorobotics, among others. Additionally, this technology can reduce the likelihood of failure at later stages of the new medication improvement process since it can be used to construct more predictable drug screening platforms at a lower cost than conventional screening methods used for pharmacological products and devices. The 3D Printing technology has received more attention in recent years in novel drug delivery

Fig. 2. Orodispersible film [17]

Fig. 3. FabRx's pharmaceutical 3D printer for personalized medicines, M3DIMAKER [21]

approaches due to its many inherent advantages over the conventional technologies, including a customised and individual formulation with adjusted dose, fabrication of highly accurate solid dosage forms on-demand manufacturing, more mechanised, quick and simple to use, and cost-effectiveness. This is supported by various scientific databases, including Scopus, MEDLINE, EMBASE, and Pub Med" [18].

3D printing innovation is getting more open to drug researchers and the first 3D printed tablet Spritam was endorsed by FDA in Aug 2015.

"One of the different 3D printing techniques, only Fused Deposition Modelling (FDM), Semi-Solid Extrusion (SSE), Binder Jetting (BJ), and Selective Laser Sintering (SLS) have been used for pediatric drug dosages [19]. FDM is a popular choice because of the low cost of printers, high-quality printouts, and the ability to use drug-containing filaments through hot-melt extrusion (HME)" [19].

Due to its potential benefits, such as improved productivity, complicated drug release profiles, multiple dosing, single-step processes at low cost, and customization/personalization of drug administration, 3D printing has been widely used in the pharmaceutical industry.

3D printing technology enables the creation of customized drugs with tailored dosages, sizes, shapes, and release properties, thus making personalized medicine a possibility. However, further advancements are necessary to ensure that commercial 3D printers comply with Good Manufacturing Practices (GMP). Additionally, a deeper understanding of fabrication processes and materials, including API stability and non-pharmaceutical-grade excipients, is needed to meet regulatory standards.

Furthermore, 3D printing's short-run properties are well-suited to patient-specific drugs, which are becoming increasingly popular as personalized medicine becomes more prevalent. The technology can also accelerate the clinical trial process by rapidly producing small batches

of drugs with varying compositions. Companies can create multiple versions of a drug for different populations and manufacture them in short-run batches using 3D printing [20].

2.4 Chewable Formulations

Chewable formulations, including chewable tablets, soft-chews, and chewing gum, are designed to help break down and dissolve the Medicament in the mouth. These products have several advantages, including easy administration without the need for water, potential assistance with swallowing, and an attractive appearance that may be preferred by patients. However, chewable products have limitations in terms of taste masking and controlled release through coating techniques due to the significant mechanical stress they undergo during administration. Furthermore, the effectiveness of drug release and therapeutic outcomes may vary depending on the patient's chewing ability [6].

E. Kimaro et al. had "Formulated of chewable albendazole tablets with improved dissolution rate. It was found that assay of the best formulation is 99.23% which was within the in-range assay specification 95–105%. Dissolution single point in 30 min was found to be 91.5% disintegration between 2-5 min and friability 0.45%" [22].

Fernando Perez *et al*. had demonstrated "acceptability increased with age and some acceptability issue remain for the younger children. Nevertheless, this formulation was considerably better accepted than the conventional tablets regardless of treatment in young children.Chewable formulation appears to be an appropriate alternative to the hard tablet of mebendazole for treatment of STH and preventive interventions in children aged 2 to 4 years" [23].

2.4.1 Application of chewable tablets

1. Local therapy: Chewable tablet can release an active substance at a controlled rate over an extended period of time providing a prolonged local effect.

2. Pain: "Successful treatment of minor pains, headaches, pains of cold, muscular aches, etc. requires rapid absorption of therapeutic doses of the active substance. Chewable tablet as a drug delivery system could be beneficial in minor pain treatment, when buccal absorption results in fast onset of action and reduces the risk of gastrointestinal side effects. 3. Systemic Therapy: Chewable tablet provides benefits to systemic drug delivery, especially if the active substance is absorbed through the buccal mucosa" [24].

2.5 Strategies to Improve Patient (Pediatric) Compliance

- "Current developments have been focused on the design of dry solid formulations to be converted to liquid at the point of administration" [14].

- "One of the major limitations of liquid products with regard to patient acceptability is the lack of controlled release formulations resulting in the need to administer multiple doses throughout the day. A number of approaches have been investigated for the development of sustained release liquids, such as ion exchange resins, coated micro particles in suspension or drug microemulsions. few sustained release liquid formulations are available in the market such as azithromycin extended release (1st) and methylphenidate hydrochloride extended-release oral suspension" [14].

- "Recent work has been directed towards the investigation of appropriate vehicles for pediatric formulations with improved palatability. For example, milk has been explored as a vehicle in liquid formulations showing potential for solubilizing drugs while maintaining the stability of the emulsified vehicle. The use of milk as a vehicle for the administration of drugs was also at the background of the development of a 'nipple shield' delivery system which is designed to accommodate a drug-loaded insert delivering the API into milk while breastfeeding neonates" [14].

- "conventional solid forms may not be suitable for patients with swallowing difficulties, in particular for pediatric populations. Administration devices such as 'pill swallowing cups' have been used to increase the suitability of tablets and capsules of relatively large size to a broader population range" [25].

- MEDICATED DOSING STRAW – "If the liquid is bitter or the large tablet hard to swallow then it enables the administration of granulated medication, since it is already precisely pre-dosed in a straw. The patient tears open the sealed single pack, takes out the straw puts it into his favorite drink, takes off the end cap and sucks. The straw contains a so-called controller, which goes up when drinking the medicine. Once the total dose is taken, the controller stays at the top" [26].

- "The development of the solid dosage pen is another novel drug delivery, which consists of a cylindrical rod manufactured by mass extrusion and incorporated into a pen-like device. Using this handy device, dosing adjustments can be easily made by cutting small tablet-like slices of the required length" [25,27].

3. OFF-LABEL MEDICINES FOR PEDIATRICS AND NEED OF REGULATIONS

One prevalent type of off-label medication involves the prescription of existing, commercially available drugs for an indication or symptom that has not received approval from the Food and Drug Administration (FDA). This results in the medication being used off-label, meaning it is not listed in FDA-required drug-labeling information and lacks FDA approval for the specific use [28].

Off-label medications refer to the prescription or administration of drugs outside the recommended route, dose, and indication specified on the package label, which is different from labeled medications. Unlicensed medications, on the other hand, are formulations or dosages that have not been approved in the country where they are prescribed or administered. Off-label medication types include prescribing drugs outside the approved dosage form, strength, frequency, and route of administration, or administering them in contraindicated situations or out of the recommended age range. Pediatric patients are particularly susceptible to severe overdose and incorrect dosing when using off-label medications. Off-label medications are administered using different techniques, such as cutting tablets, segmenting transdermal patches, and forming solutions or suspensions using solid or liquid dosage forms. Although off-label medication use is common for all age groups, it is most commonly used for pediatric populations, with approximately 60% of pediatric formulations being prescribed in an off-label manner [29].

When drugs are approved for marketing, it's based on their safety for specific indications, as determined by clinical studies that establish a positive benefit-risk ratio. However, it's impossible to identify all potential uses of a drug during the approval process, which means that it won't be approved for all possible indications, dosage forms, routes of administration, or age groups (such as children, pregnant women, and lactating mothers). Consequently, the practice of off-label use is common worldwide, with usage as high as 90% in the pediatric population and 40% in adults. In a recent survey of 160 commonly prescribed medicines in the USA, off-label use was found to be 21% overall, and as high as over 80% for some drugs [30].

Many pediatric guidelines suggest NSAIDs or paracetamol for pain, fever or inflammation in children they should be taken with caution due to the possibility of adverse reactions such as hypersensitivity reactions renal damage, and even kidney failure. However, the reporting of recommendations on NSAIDs in pediatric guidelines is inadequate, which is due to several reasons and may potentially lead to inappropriate drug use [31].

Pediatric patients may be uniquely vulnerable to adverse events related to excipients, due to immature absorption, distribution, metabolism, and elimination pathways. Off-label use of drugs formulated for older populations remains prevalent, as clinical studies that meet regulatory approval standards are scarce [29,32]. The use of adult medications in children for purposes not approved by regulatory authorities may have unintended consequences. One such consequence is the potential exposure of pediatric patients to excipients that could be harmful. Excipients are an essential component of pharmaceutical formulations, but some may be safe for adults yet toxic to children due to the lack of safety data on pediatric doses. This toxicity is not always related to the dose, age, or route of administration, but rather to the physiological and pharmacokinetic differences between children and adults. Pediatric patients may be especially vulnerable to the effects of excipients due to their immature physiological condition and heightened sensitivity to chemical

substances [29,33,34]. Therefore, a wide-ranging safety evaluation of excipients in a pediatric pharmaceutical preparation is necessary before use; referring to accessible safety data from adult human and animals as well as safety data from pediatric use and juvenile toxicity studies.

Children are sometimes described as "therapeutic orphans," as they face unnecessary risks and do not benefit from the latest therapeutic advances [34]. Despite the development of a pharmaceutical regulatory framework that aims to ensure high standards of safety, quality, and efficacy of drugs for use in adults, children have been historically deprived of adequate testing and authorization of medicines. In fact, past "drug disasters," such as the tragedies involving sulphanilamide and thalidomide, which mainly affected children, were instrumental in the creation of such a framework.

The Pediatrics Regulation was put into effect in the European Union in 2007 to increase the accessibility and development of paediatric pharmaceuticals. This rule makes sure that these items are legitimately approved for use in paediatric populations and provide more details about how to use them in various age ranges. As a result, since 2007, paediatric development for new drugs as well as any new indications, administration techniques, or pharmaceutical formulations of already-existing products that have a supplemental protection certificate or a patent has been required in the European Union. Unless the European Medicines Agency grants a product-specific or class exemption, a Pediatric Investigation Plan (PIP) is often required to meet this criterion. By complying with this regulation, the product becomes eligible for the incentive component of the legislation [35,36].

Since 1997, there have been legal and administrative safeguards in the United States to address the creation of items for kids. The Best Pharmaceuticals for Children Act (BPCA), the present law, provides incentives but does not impose any requirements. On the other hand, the Pediatric Research Equity Act (PREA) does not offer incentives but does specify the conditions under which paediatric development must be carried out. Under Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA), both statutes were modified and made permanent in 2012 [37].

BPCA The Best Pharmaceuticals for Children Act (BPCA) provides financial benefits to companies in the form of additional marketing exclusivity. The FDA grants a six-month extension of an existing patent or exclusivity for the entire active ingredient if the sponsor conducts the studies requested in a Written Request (WR). This second period of exclusivity only applies to the particular product that was studied. Although sponsors may voluntarily participate in the requested studies, they must meet the conditions established by the FDA. To request a WR, sponsors can submit a Proposed Pediatric Study Request (PPSR). It should be noted that the FDA will not grant pediatric exclusivity or issue a WR for studies that have been submitted to the agency prior to the issuance of the WR. The requirements for qualifying for pediatric exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act are detailed in the 1999 Guidance for Industry, which is currently being updated. Additional information on the BPCA-Written Request process is provided in a question-and-answer format to assist sponsors.

In specific cases, the Pediatric Research Equity Act (PREA) mandates that drug and biological product sponsors conduct research to evaluate the safety and effectiveness of their new products in pediatric patients. The FDA may grant a waiver for this requirement. PREA applies to new products, which includes those with a new indication, active ingredient, dosage form, dosing regimen, or route of administration. However, these studies are only required for the approved indications in adults. As part of any PREA-regulated product development program, sponsors must submit an initial Pediatric Study Plan (iPSP), which is intended to identify necessary pediatric studies early in the product development process and plan accordingly. Biosimilars are also subject to PREA requirements, except for those with orphan designation. As part of any marketing application subject to PREA, sponsors must submit an agreed-upon iPSP. If a pediatric development program is not appropriate, this should be discussed with the FDA at this stage [35,38].

4. LEGISLATIVE OBLIGATIONS AND REQUIREMENTS

4.1 European Union

The European Union (EU) also mandates that orphan-designated products fulfill the same requirements, except for generic, hybrid, or biosimilar biological products, traditional herbal and homeopathic products, and those authorized

using the "well-established use" legal basis. In the EU, complying with the obligation to agree to a Pediatric Investigation Plan (PIP) and conduct pediatric studies is linked to receiving a reward or incentive. Sponsors who fulfill the requirement may be eligible for a 6-month extension of the patent (SPC) or a 2-year extension of market exclusivity for orphan-designated products. To further encourage pediatric product development, a new marketing authorization, the Paediatric Use Marketing Authorization (PUMA), was introduced. PUMA is granted for products exclusively developed for use in pediatric patients, in compliance with an agreed PIP. Such products benefit from 10 years of data exclusivity, meaning no one can use the data generated by the sponsor to support the authorization of a similar product for 10 years.

4.2 United States

The Pediatric Research Equity Act (PREA) mandates that certain drug and biological products undergo pediatric studies. New drug applications (NDAs) and biologics licensing applications (BLAs), including supplements, for

Table 1. US and EU drug development process

	US BPCA	US PREA	EU
Development	Optional	Mandatory	Mandatory (optional for off-patient)
Instrument	Written request	Pediatric study plan (PSP)	Pediatric investigation plan (PIP)
Waiver	Not applicable	3 grounds	3 grounds
Timing	End of phase 2	End of phase 2	End of phase 1
Rewards	6-month exclusivity	None	6-month spc extension Patent
New Application (505)	Yes, with exclusivity	yes	yes
Biologics	yes	All	All
Orphan	Included	Excluded	Included
Decision	FDA	FDA	EMA(PDCO)

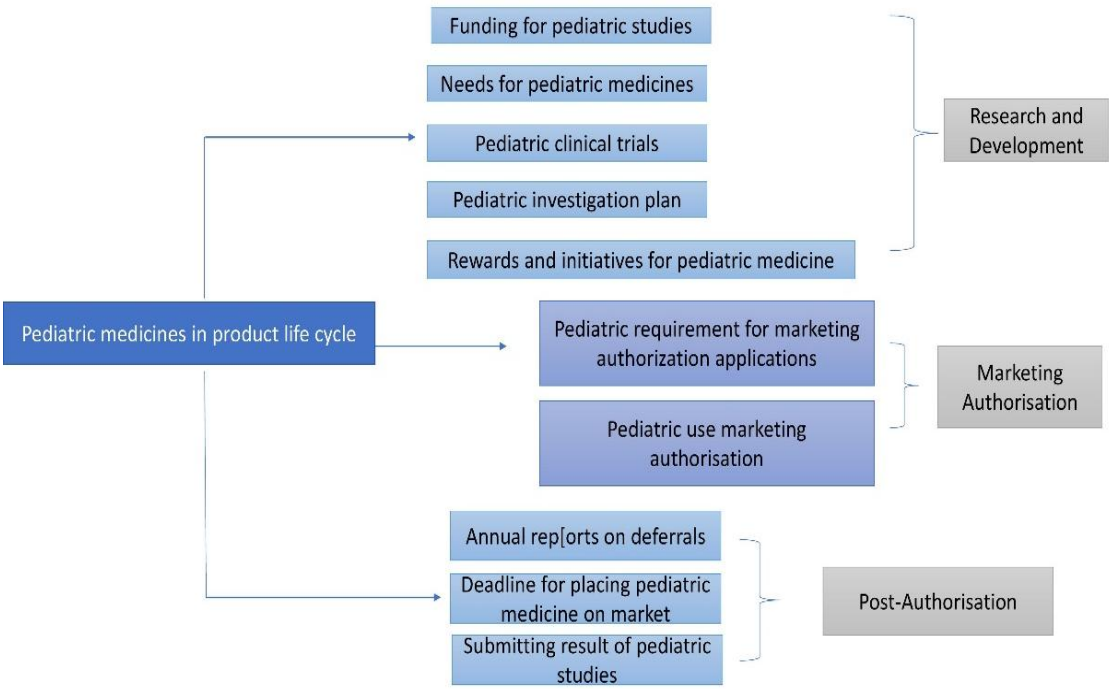

Fig. 4. Product life cycle of pediatric medicines

new active ingredients, indications, dosage forms, dosing regimens, or routes of administration must comply with these requirements. Sponsors may apply for a waiver to avoid conducting the studies, and under certain conditions, the FDA can request a pediatric assessment from holders of applications for previously approved marketed drugs or biological products.

In the US, the requirement and incentive for pediatric studies are distinct and independent processes. Complying with PREA alone does not qualify for exclusivity, unless the study required under PREA is the same as the study agreed upon under the Best Pharmaceuticals for Children Act (BPCA). To qualify for pediatric exclusivity in the US, the FDA must issue a Written Request (WR) specifying the desired studies. The procedures for obtaining a WR are described in the Incentives and Rewards section [35].

5. CURRENT STATE AND CHALLENGES IN EXCIPIENTS REGULATION IN INDIA FOR PEDIATRICS

The Drug and Cosmetics Act 1940 and Regulations 1945, which are administered by both the Center and State governments, are listed in the Indian constitution as one of its most significant sections that deals with both drugs and health. Only excipients claimed or rated in the Indian Pharmacopoeia are under the Food and Drug Administration's regulatory oversight in India. The Indian Pharmacopoeia's approval of drug goods, including excipients, is primarily under the authority of the Central Drugs Standard Control Organization (CDSCO).

The Drugs and Cosmetics Act's Schedule Y establishes a particular paediatric clinical testing category that must be adhered to. To guarantee the production and distribution of excipients of the highest possible quality, auditing and monitoring of excipient manufacturing and supply chains are required. Since 1991, several regions of the world have developed the International Pharmaceutical Excipients Councils (IPECs) [39].

5.1 Current Scenario in India

Clinical trials and protocols created for healthy adult people provide the foundation for paediatric medication development in India. Clinical practices in India mainly relies on safety and efficacy data released in other developed nations, as well as inferences taken from dosages used for adults. Children's medications are not subject to any precise restrictions, thus doctors, nurses, and other caretakers must estimate dosages by crushing tablets or diluting liquids. This approach may result in incorrect dosing, endangering the medication's safety and effectiveness..There are no specific regulations for conducting trials in the pediatric population, and the lack of such regulations may result in the Indian pediatric population being used as adults by drug companies.

In India, there are also no specific regulations for the excipients used in medicinal goods. Excipient information is not listed on the label (apart from preservatives, colours, and alcohol, depending on the content), which could be problematic if there are any safety concerns. Although Indian drug regulators have acknowledged the need for regulation given the paediatric environment in India, information on pharmaceutical excipients for products is only readily available for those products included in the National List of Essential Medicines, the WHO's Model List of Essential Medicines for Children, and the Model Formulary for Children [39,40].

5.2 Challenges

- Lack of evidence-based safety data considering physiological, toxicokinetic, and toxicodynamic Changes in pediatrics.
- Lack of evidence-based safety data for the special population (i.e., preterm neonates, patients with specific disease).
- A safety evaluation of excipients in not only a pediatric formulation but also off-label used products is necessary before use referring to accessible safety data.
- Accessible data are from adult human and animals, safety data from pediatric use and Juvenile toxicity studies will be required [39].

6. EFFECT OF PEDIATRIC REGULATION

In July 2000, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) took the first coordinated action in regulating drugs for children. This was accomplished by adopting the ICH E11 guideline, which aimed to promote timely development of

paediatric drugs worldwide and provide guidance on critical issues and ethical considerations related to paediatric drug development. Although the guideline became a valuable tool for designing clinical studies for children, it was not mandatory and had little impact on paediatric drug submissions in Europe and globally. Despite this, an update to the guideline has been deemed necessary due to advancements in paediatric medicine development, and initial work has commenced in this regard [41].

Over the first nine years since its inception, the Paediatric Regulation has had a positive impact on the development of drugs for children, as indicated by the collected data. The regulation includes a system of obligations and rewards that has been effective in promoting the development of medicines for children, resulting in a high number of agreed PIPs, paediatric clinical trials, and new drugs. However, it has become evident that incentives alone are not enough to encourage voluntary paediatric research into off-patent medicines of interest to children, as only two PUMAs have been authorized. Furthermore, of all anti-cancer drugs, only 14 have proposed PIPs for the study of cancers that specifically affect children or are not studied in adult patients. By the end of 2016, more than 130 PIPs had been completed, and over 800 were still ongoing, with various factors impacting their completion timelines, including the rarity of the disease and the availability of other off-label treatments for the same condition. In the latest period from 2014-2016, 74 new drugs were authorized for paediatric use [42].

7. CONCLUSION

There are many different drug delivery methods and strategies to improve child compliance, but when developing a drug for children, there are a number of variables to take into account, including age, pharmacotherapy-related aspects, including drug administration skills (ADME), drug-related toxicity and adverse effects, safety, and child taste preferences. Pediatric guideline documents provided by regulatory bodies should be followed for the safety and effectiveness of paediatric dosage forms.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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