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A Comprehensive Review of Pediatric Drug Development: An Extensive Analysis of Present Difficulties and Prospects for the Future

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Abstract: Creating a suitable dosage form for pediatric medical treatment can be challenging, considering factors like body weight, taste masking, excipient safety, and dosage form size. Potential options such as mini-tablets, soluble films, and oral disintegrating tablets have shown promise. However, pediatric dosage forms face challenges such as age-related physiological changes, excipient safety concerns, technical demands, limited profitability, clinical trial constraints, and unclear legislation. Recent advancements have increased pediatric formulation acceptance, providing parents with easier administration and greater dosing flexibility. Key considerations include acceptability, palatability, pediatric compatibility, excipient selection, and modified drug release formulations or fixed-dose combinations. Machine learning classifiers to predict bitterness in pediatric formulations could be explored. The shift in the paradigm of pediatric medication development involves a "carrot-and-stick" strategy, addressing population-specific issues. This includes leveraging nanotechnology-based delivery systems encompassing lipid-based, polymeric, and inorganic nanoparticles. An essential aspect is involving a diverse workforce, including pediatric patients, caregivers, healthcare stakeholders, drug developers, and physicians, to establish standard criteria for pediatric drug development. This paper aims to compile information on the current status of pediatric drug development by providing an overview of the historical regulatory environment, summarizing challenges in pediatric drug formulation, and analyzing the pros and cons of innovative methodologies in pediatrics.

Keywords: drug development; nanotechnology; pediatrics; safety concerns.

1. Introduction

The study of children and adolescents' physical, social, and mental health is known as pediatrics. There are several subgroups within the pediatric population: preterm new-borns, term and post-term new-borns, babies and toddlers, children, and adolescents. However, the assessment and creation of age-appropriate treatment programs may be hampered by the lack of agreement on the maximum age for pediatric patients.

To combat the pervasive and possibly dangerous practice of off-label use of medications permitted for adult use but recommended for pediatric patients, appropriate pediatric pharmaceuticals must be developed. Obstacles, including dosage flexibility, swallowability, palatability, and the many physiological developmental phases that the

pediatric population experiences, impede the advancement of pediatric formulation development. To address dosage flexibility and give ease of swallowing, oral minitablets, micro particles, granules, liquid formulations, and scored chewable tablets have been proposed. Nonetheless, one in four active pharmaceutical ingredients (APIs) have a very bitter taste, which can cause medication interactions with taste receptors and make palatability a serious problem. This difficulty is particularly common with medications that must be taken often and in large quantities, such as anti-infectives. In these cases, the issue is made worse by the abundance of APIs that have unpleasant tastes.

In the past, children have been labeled as "therapeutic orphans," and adult medicine has been prescribed off-label due to the variability in the pediatric population and the small number of participants in clinical studies [1]. The notion that children may be thought of as little versions of adults has been challenged by the fact that children are in various developmental, physiological, and metabolic phases. It is not appropriate to immediately transfer dose forms and dosage strengths from adults to children due to the influence on the pharmacokinetics and pharmacodynamics of API. The development of pediatric medicine is receiving more attention in order to guarantee the approval and accessibility of high-quality, customized medications for children. Nevertheless, one of the difficulties in creating age-appropriate pediatric medications is not knowing which ones are safe for young patients. Global regulatory organizations acknowledge the necessity of developing formulations tailored to certain age groups and body weights for various pediatric illnesses. The Pediatric Regulation (EC) number 1901/2006 and the formation of pediatric expert committees have brought more attention to medication composition and dosage [2].

In order to securely deliver dosages, lower drug administration mistakes, improve medication adherence, and improve therapeutic results, pediatric medication development is crucial. Formulators prioritize dose forms for distribution, although they may adjust if challenges exceed benefits. As it is the least intrusive, causes no discomfort, and requires no specialized training, the oral route is the most effective way of administration for children. Solid dosage forms are typically the most feasible and reasonably priced for oral administration among adults. Modifying adult dose forms supply the pediatric medication market since pharmaceutical corporations do not find it as appealing as adult dosage forms. In order to create innovative medication delivery systems, manufacturers and researchers must work together. The future of medication distribution for newborns and pediatric patients appears bright, with a growing body of research aimed at enhancing patient compliance. In order to address the therapeutic deficiency and provide age-appropriate formulations that optimize efficacy, design quality, promote safety, limit hazards, and boost patient adherence to treatments, a strategic workforce has been assembled. Parenteral administration should only be used in more severe situations; oral administration is the most recommended method. Planning a pediatric oral formulation might be difficult since it involves selecting the right excipients, dose, and palatability. The "Safety and Toxicity of Excipients for Pediatrics" (STEP) database was developed as a consequence of the cooperation between the US and EU Pediatric Formulation Initiatives (PFIs) [3]. Its goal is to identify excipients that are suitable for use in pediatric medication formulation.

Furthermore, potentially inappropriate drugs for pediatric use have been made available by the "Key Potentially Inappropriate Drugs in Pediatrics" tool (KIDs) List. The main objectives of this list are to reduce severe adverse drug reactions (ADRs), improve care quality, save costs, and identify pediatric population research subjects. Clinical trials and licensed

medications for the pediatric population are still limited despite attempts to produce age-appropriate medical devices and pediatric pharmacological formulations. The scientific community is excited about nanotechnology because it has the potential to lower toxicity, improve targetability to particular organs, combine diagnostic and therapeutic tools in one nano carrier, and maybe shorten treatment regimens. The European Parliament views Advanced Therapy Medicinal Products (ATMPs) as "therapies for the future."

In this literature review, the historical paradigm in pharmaceutical medication development for pediatric patients is outlined (Figure 1), along with the benefits and drawbacks of employing novel treatments, including ATMPs and nano medicines, to treat pediatric diseases utilizing a fit-by-design methodology. While it is desirable, normal testing methods may not always be able to provide effective taste masking of pediatric pharmaceutical formulations.

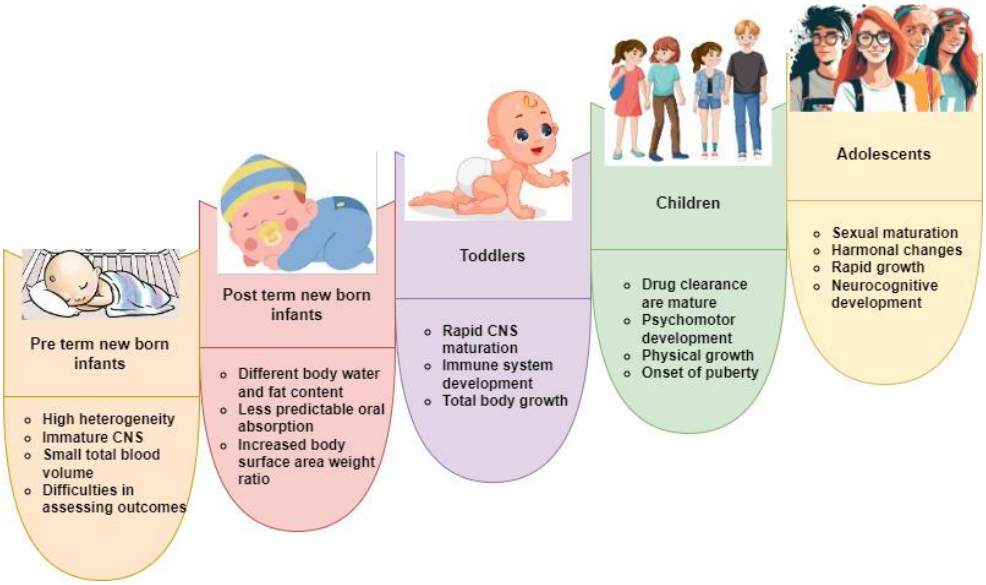

Figure 1. Age classification of pediatric patients.

2. Oral Solid Dosage Form

A finished medication product ingested, digested in the digestive system, and absorbed into the circulation is known as a solid dose form (SDF) (Figure 2). It has benefits, including minimal production costs, long-term stability, accurate dosage, and simplicity of handling and transportation. However, because of the possibility of choking or inhaling, it is not recommended in children. A two-pronged approach is being employed to solve these problems: creating dose forms for target groups and discovering cutting-edge medication delivery tools. Smaller tablets and capsules are becoming more popular as substitutes for conventional solid dosage forms since they make swallowing simpler and offer greater dosing flexibility. Flexible solid oral dose forms, such as chewable, soluble, and orodispersible tablets, are recommended by the World Health Organization (WHO) as the most suitable for pediatric patients [4]. The goal of the European launch of the Labelling of Enalapril from Neonates up to Adolescents (LENA) effort was to develop and evaluate a new, age-appropriate solid oral enalapril formulation that would qualify for a pediatric use marketing authorization (PUMA) [5]. Pharmaceutical formulations given orally in the form of tablets, capsules, or powders are known as oral solid dosage or OSD.

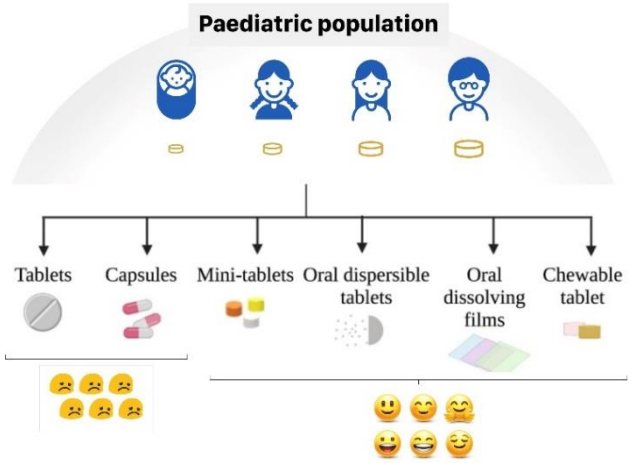

Figure 2. Different types of solid dosage forms for pediatrics.

2.1. Minitablets.

Minitablets are classified as multi-particulate drug delivery methods since they are solid oral dosage forms having a diameter of less than or equal to 3 mm. They can be crushed into bigger tablets or contained in capsules, providing dosage flexibility and obviating the need for repeated tablets. They are available in standard coated and uncoated forms as well as oro-dispersible mini-tablets, which are beneficial for patients who have trouble swallowing. As per the European Medicines Agency (EMA) released guidelines for developing age-appropriate formulations, minitablets have become increasingly popular [6]. The ability to provide customized dosages depending on age, weight, and condition has led to the widespread acceptance of oral disintegrating micro tablets or mini oral dispersible tablets (ODTs).

Minitablets were developed to facilitate the administration of medications to pediatric patients; research indicates that babies between the ages of six and twelve months can easily down a single 2 mm minitablet. They may be produced simply as modified release formulations by 3D printing, hot melt extrusion, and compression. There is no need for extra excipients when using other multi-particulate systems like granules and pellets as they are solid and do not require stabilizing agents. After being enclosed in capsules or sachets, they can be reconstituted in liquids such as milk, water, fruit juices, or soft foods. Small tablets are intended to improve medication delivery systems by lowering the dosage frequency and increasing the drug's localization. Due to their convenience in swallowing, they are especially helpful for kids and the elderly.

2.2. Oral dispersible tablets.

Due to their improved therapeutic effects and greater bioavailability, oral dispersible tablets (ODTs) are becoming more and more popular with pediatric patients and healthcare providers. ODTs avoid hepatic first-pass metabolism by dissolving in the mouth and undergoing pre-gastric absorption from several esophageal sites [7]. They have a quick start of action, are more easily administered, have exact dosage, are more palatable, have greater bioavailability, and are more economical. ODTs replace functional excipients like preservatives by improving swallowability and stability. They do not, however, provide much dosing flexibility. ODTs are a type of solid oral dose form that dissolves quickly in the mouth without water, making them especially advantageous for patients who have trouble swallowing regular tablets or capsules. Fast disintegration and dissolution, enhanced patient compliance, adaptability in dosage and formulation, fewer dose intervals, and less toxicity are some of

ODTs' main benefits. Solid dispersion techniques, lyophilization, and direct compression are common production processes for ODTs. Disintegration time, dissolution, mechanical strength, and stability are among the evaluation criteria for ODTs. The solid-state characteristics of the formulation are also evaluated using differential scanning calorimetry (DSC). Overall, ODTs are a great alternative for enhancing medication administration, particularly for patient populations that have difficulty swallowing, and they provide a number of advantages over traditional oral solid dose forms.

2.3. Oral dissolving films.

Advanced oral dose forms called oral dissolving films (ODFs) are made to dissolve quickly or in the mouth without the need for water. They can have both local and systemic effects, and they are meant to be administered buccal. ODFs have several benefits, including enhanced bioavailability, self-administered, cost-effectiveness, and high patient compliance; they also avoid first-pass metabolism and have better accessibility, administration, and retention. Hydrophilic polymers and other excipients are used in the solvent-casting process, one of the common manufacturing processes for ODFs. The films' rapid disintegration is intended to release the integrated active medicinal components in a matter of seconds. Due to their many advantages over conventional oral dose forms, they have the potential to be a huge market and business opportunity.

Disintegration time, dissolution, mechanical strength, and stability are important factors in evaluating oral dissolving films. The solid-state characteristics of the formulation are also evaluated using methods such as DSC. All things considered, oral dissolving films are a fresh and exciting method of delivering drugs orally while also improving patient convenience, adherence, and treatment results. In recent years, ODFs have shown great promise as a patient-compliant dose form, particularly for kids with asthma and people suffering from schizophrenia and dysphasia [8]. ODFs provide a number of benefits, such as being simple to take, having precise and practical dosage, not requiring water when administered, avoiding hepatic first-pass metabolism, acting quickly with improved bioavailability, and being reasonably priced.

2.4. Chewable tablets.

Chewable tablets, with their smooth texture, agreeable flavor, and convenience of administration, are a popular and handy dose form for juvenile and geriatric patients. They may be given with water, have a smooth texture and good absorption, and are reasonably priced. Chewable pills, on the other hand, are not very good at controlled medication release or flavor masking, nor do they provide dosage flexibility. Children two years of age and up can safely handle these; however, some could mistake them for candies. Chewable tablet preparation involves compression and proprietary technology; dissolving agents are not used [9]. They provide a number of benefits, including the stability of solid dosage forms, ease of ingesting, and oral drug administration without the need for water. They offer a practical method of medication distribution for a range of healthcare markets and are especially advantageous for pediatric populations. To guarantee the efficacy and safety of chewable tablets, the Food and Drug Administration (FDA) places emphasis on crucial characteristics, including hardness, disintegration, and dissolving. It's critical to identify on the label which medications are easy to chew and which ones require chewing and/or crushing before swallowing in order to release the active component.

3. Excipients in the Pediatric Formulation

Excipients are natural or synthetic materials used in dosage forms with active ingredients (Figure 3), accounting for over 90% of the total weight of each drug. They represent 0.5% of the global pharmaceutical market and are used in pharmaceutical formulations as wetting agents, volume or weight extenders, diluents, emulsifiers, taste enhancers, preservatives, and solvents. They also serve as absorption enhancers. Excipient selection for pediatric formulation is a crucial and difficult task that requires the evaluation of several factors to ensure they are acceptable to use in the formulation. Factors such as weight, age, improper organ system development, the absence or presence of certain enzymes, and their numbers appearing in the pediatric population can influence excipient metabolism. Rapid growth and development in children cause changes in the composition of lipids and fluids in the body, as well as changes in various body organs, binding of drugs to body proteins, active transport mechanisms, and metabolic pathways.

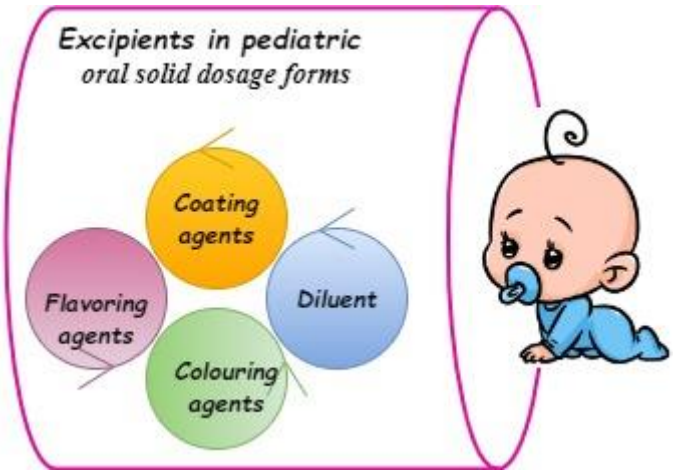

Figure 3. Excipients used in the formulation of pediatric solid oral dosage forms.

Dosage forms like pills and tablets are regularly adjusted in ineffective ways to offer safe, efficient, and consistent dosages. Healthcare professionals and compounding pharmacists can be of assistance, but results may be variable due to different approaches and may not always be accessible, especially in underdeveloped nations. Patients often use strategies such as division of doses, dissolving drugs by crushing them in liquids, and administering medications at levels that are not thoroughly evaluated. The selection of safe excipients for pediatric dosage form formulation is not only an important phase but also one of the difficult processes, as the pediatric population is physiologically distinct from the adult population in several respects. The European Medicine Agency (EMA) guideline serves as a decision-making tool for assessing the safety profile of excipients [10]. In the pediatric formulation, the excipients must be inert, safe, and of the required quality. However, the necessity of excipients does not undermine their toxic effects. The European Pediatric Formulation Initiative recently created the STEP, a Pediatric database that compiles information about the toxicity and safety of excipients used for pediatrics.

Pediatric formulations often use excipients that can be toxic or problematic for children, particularly neonates and young children. Common adult formulations include propylene glycol, ethanol, benzyl alcohol, parabens, and lanolin. Safer alternatives for pediatric use include starch, dehydrated calcium hydrogen phosphate, erythritol, cellulose powder, mannitol, aspartame, and sucrose. Common preservatives in pediatric solid and semi-solid formulations include benzalkonium chloride, methyl parahydroxybenzoate, and propyl

parahydroxybenzoate, which are also considered toxic in neonates. Propylene glycol is still included in some pediatric formulations and requires caution, especially in children under 4 years old and neonates. Microcrystalline cellulose, methylcellulose, and ethyl cellulose are commonly used excipients in pediatric solid formulations with no major side effects, but high amounts can cause laxative effects. Flavoring agents like grape essence, lemon, caramel, and orange are often added to improve palatability, but their complex compositions can be a concern.

3. Diluents

Diluents are fillers used to increase the bulk content in dosage forms when the active element is insufficient. Common diluents include lactose, starch, and microcrystalline cellulose. Lactose is commonly used to manufacture capsules, tablets, lyophilized powders, and powder inhalers, but it can cause hypersensitivity reactions in children and infants. Due to their similar flow and disintegrating properties, other diluents like dehydrated calcium hydrogen phosphate, starch, cellulose powder, and erythritol may be used in pediatric formulations.

Starch is a versatile excipient with many properties, serving as a diluent, binding agent, and disintegrating agent in solid dosage forms. However, it needs to be stored in a dry environment due to its microbial susceptibility. Microcrystalline cellulose is a white, porous powder that is odorless, non-toxic, and non-irritating. It acts as a disintegrating and lubricating agent in tablet preparation and as a binder, thinner, and lubricating agent in tablet and oral capsule formulations.

Diluents, like tablets, are inert substances added to pharmaceutical formulations to increase dosage forms' weight, volume, or size. They play a crucial role in improving content uniformity, enhancing tablet properties such as cohesion and flow, and promoting better formability. Common diluents include starches, hydrolyzed starches, partially pregelatinized starches, anhydrous lactose, lactose monohydrate, and sugar alcohols like sorbitol, xylitol, and mannitol. Diluents must meet specific criteria to ensure safety and effectiveness, such as being non-toxic, commercially available in acceptable grades, physiologically inert, and chemically stable independently and combined with active pharmaceutical ingredients [11]. They are often used as dry binders to provide tablets with high strength.

4. Coating Agents

Coating agents are essential in pharmaceutical formulations to enhance the acceptability and palatability of drugs. They are used to apply a coat over the surface of dosage forms, making it easier for patients to swallow, enhancing stability, protecting the dosage form against the gastrointestinal environment, increasing mechanical resistance, and allowing for the formulation of a dosage form with a modified release. Phthalates, which are used as film-forming agents, coating agents, or plasticizers, are the main function of these agents.

Phthalate exposure during pregnancy has been linked to congenital disabilities, and it is recommended to avoid phthalates like DBP (Dibutyl phthalate) and DEHP (di-(2-Ethylhexyl) phthalate) in the pharmaceutical sector [12]. Coating agents are used to coat various pharmaceutical solid dosage forms, such as tablets, pellets, granules, capsules, powders, and crystals. They serve several purposes, including increasing stability, masking unpleasant tastes or odors, improving swallowability, distinguishing the product during

manufacturing or patient use, minimizing interactions between incompatible components, providing mechanical integrity, and modifying drug release.

Common coating agents used in pharmaceuticals include polymers, plasticizers, solvents, and coloring agents. They can also be used in food applications to enhance appearance, preserve freshness, and prevent spoilage. The selection and formulation of coating agents are critical aspects of pharmaceutical product development, as they can significantly impact the performance and stability of the final dosage form.

5. Sweeteners

Sweeteners are crucial in improving the flavor and palatability of pharmaceutical products, especially in oral pediatric formulations. The concentration and choice of sweetening agents in formulations are influenced by the type of APIs and the requirement of flavoring agents. Sweeteners have been associated with photosensitivity responses, diarrhea, and insufficient nutritional absorption, which can pose health and safety issues.

Sucrose, sorbitol, mannitol, aspartame, and sucralose are the most commonly used sweeteners in medicinal formulations. Natural sweeteners like sucrose and fructose are high in calories and metabolize and alter as they move through the body. Sucrose is a naturally occurring disaccharide digested into monosaccharides, fructose, and glucose in the intestine. It should be avoided in formulations for children who have Type-1 diabetes, as high amounts given daily have been said to be carcinogenic [13]. Artificial sweeteners, such as aspartame, are made from chemicals synthesized or taken from naturally occurring elements and treated further. They have a high sweetening capacity and show a comparatively better safety profile than natural sweeteners, so that they may substitute sucrose-like natural sweeteners in pharmaceutical formulations. Aspartame consumption rises in oral disintegrating tablets and chewable medications, nearly 200 times sweeter than sucrose [14]. Phenylalanine is extremely dangerous to phenylketonuria individuals and pregnant women carrying a fetus with this metabolopathy. Sorbitol, a laxative in high dosages, is safe for pediatric kids because it is a monosaccharide not absorbed by the digestive system. It is also used as a capsule plasticizer and diluent. However, it may result in gastrointestinal problems such as nausea, vomiting, osmotic diarrhea, stomach pain, swelling, and flatulence. Mannitol is both a diluent and a sweetener, but it has been linked to severe allergic reactions in children. Sucralose, a chlorinated sugar, has a sweetening power of 100 to 300 times sucrose and is known as a zero-caloric sugar alternative. It can boost the expression of two cytochromes, P450 isoforms necessary for drug purification and cell flow transport proteins [15]. Artificial sweeteners, such as saccharin, cyclamate, aspartame, and sucralose, are added to pharmaceutical formulations to improve taste, stability, or solubility, enhancing patient compliance and acceptance of the medication.

6. Colouring Agents and Dyes

The pharmaceutical, cosmetics, and food industries use coloring compounds for various purposes, including customer attraction, product identification, and protection of light-sensitive items. Most colorants used in oral pharmaceutical formulations fall into four categories: xanthene dyes (quinoline yellow), azo dyes (tartrazine), triphenylmethane dyes (erythrosine), and dyes made from xanthene or xanthene derivatives. Few colorants are universally acceptable from a regulatory standpoint, as some have been associated with hypersensitivity and other

unfavorable effects in children [16]. Common side effects include asthma, urticaria, angioedema, hyperkinesis, and anaphylactic responses. Azo dye used in children is typically cross-sensitive to indomethacin, sodium benzoate, and acetylsalicylic acid (ASA). Avoiding azo-dyes in pediatric drugs or conducting risk-benefit analyses before inclusion in the formulation is advised.

Coloring agents play a crucial role in medicine, particularly in pharmaceutical formulations, as they are pharmacologically inactive substances added to drugs to differentiate between products, improve patient compliance, protect light-sensitive active ingredients, and prevent counterfeiting. Ideal coloring agents are nontoxic, stable, odorless, and compatible with the API. Regulatory bodies like the U.S. FDA and the European Union regulate the use of coloring agents to ensure their safe and appropriate use in drugs, food, cosmetics, and medical devices [17].

7. Challenges in the Development of Pediatric Dosage Forms

The development of pediatric medication faces numerous challenges, including a small and disorganized market, ethical and methodological restrictions for pediatric studies, large research expenses, and a constrained and unreliable data supply. These obstacles affect the quality, safety, and efficacy of pediatric dosage forms and physiological and formulation-related challenges (Figure 4). Consequently, only a small amount of research has been done to tailor medicines to the needs of children. Despite the large number of children affected in affluent countries, the pediatric market remains less. An estimated $20 million will go toward a pediatric development plan for a new pharmaceutical product, which might translate to a subpar, if not negative, return on investment for an already approved drug [18].

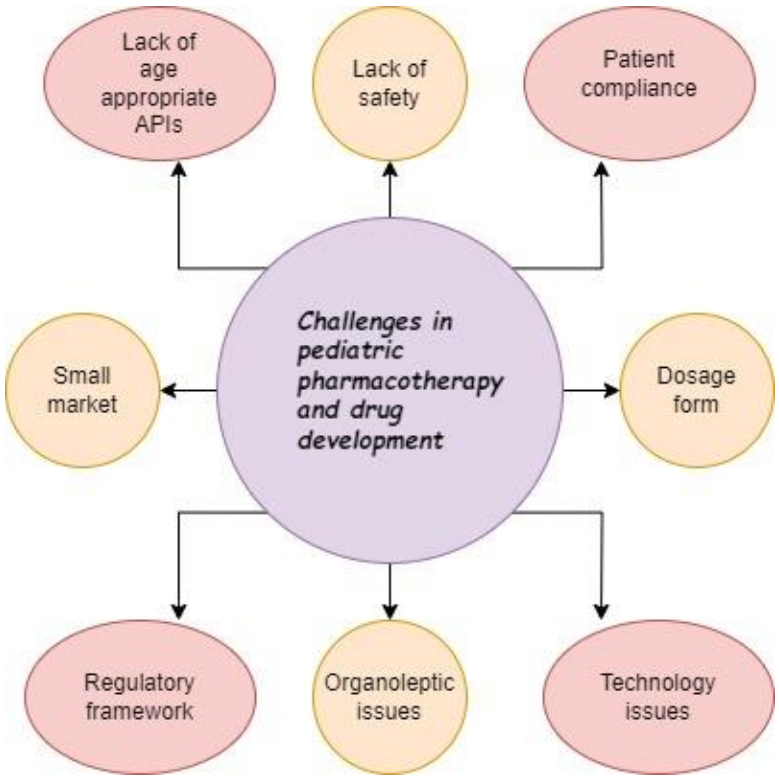

Figure 4. Factors impacting pharmacotherapy practice and drug development for pediatric patients.

Proposed EU and US legislation intends to enhance children's overall health and well-being by extending pediatric pharmaceutical product research, development, and approval. However, it is unclear if current incentives would encourage more pediatric research in the pediatric age group in Europe as the patent extension period is not better than in the United States. The choice of the most appropriate formulation for the patient's age, dosing regimen considerations, route of administration and dosage form suitability, excipient compatibility and safety, patient compliance and palatability, regulatory and clinical trial challenges, lack of standardization and availability of appropriate pediatric formulations are some of the major issues in the development of pediatric dosage forms.

In total, developing pediatric-friendly dosage forms requires careful consideration of multiple factors related to the target patient population, formulation design, regulatory requirements, and clinical evaluation to ensure safe, effective, and compliant drug delivery.

8. Pharmacological and Physiological Challenges

Pediatrics are not young adults in terms of biological or pharmacological development, but they can be divided into sub-groups based on physiological and pharmacological differences. These include pre-term new-born infants, full-term new-born infants, infants and toddlers, 2-11-year children, and adolescents aged 12-18. The development of pediatric dosage forms faces pharmacological and physiological challenges due to the unique characteristics of the pediatric population [19]. Pediatric patients' varying physiological conditions make it difficult to create formulas that specifically address the requirements of each age group. The lack of information on medication molecules in juvenile patients makes it more difficult to create formulations that work. Excipient safety in pediatric formulations needs to be carefully considered since some excipients may be harmful. Taste-masking issues arise from pediatric patients' sensitive taste, making formulations effective and palatable. Specialized technologies are often required for pediatric formulations, and low profitability is often associated with pediatric formulations. Clinical trials in pediatric patients are often challenging due to the small number of children with the same medical condition [20].

Regulatory clarity for pediatric formulations can be unclear, leading to difficulties in developing and approving these formulations. Dosing challenges arise as pediatric patients often require different dosing regimens than adults. Immunogenicity modeling and simulation challenges are also crucial in developing pediatric formulations.

These pharmacological and physiological challenges underscore the need for careful consideration of the unique needs of pediatric patients in the development of pediatric dosage forms.

8.1. Pre-term new-born infants.

Pre-term new-borns are babies born before 37 weeks of gestation, more than three weeks before their due date. These infants are at a higher risk of health complications due to their underdeveloped organs, particularly the brain, lungs, and liver, which are still growing and developing in the final weeks of pregnancy. Common complications include breathing problems, maintaining body temperature, and feeding difficulties. Pre-term infants often require special care in a neonatal intensive care unit (NICU) and may have a higher risk of developmental delays later in life. Rapid changes in pharmacology and physiology, as well as incomplete renal development and hepatic clearance processes, must be considered when

delivering drugs to pre-term pediatric patients. Protein binding and displacement difficulties, transdermal absorption, and specific new-born susceptibilities, such as retinopathy, must also be considered when delivering drugs to pre-term new-borns.

8.2. Full-term new-born infants.

Full-term newborns are more mature than preterm infants due to the competitive binding between albumin and bilirubin. This makes medications more readily available in these patients as they develop a blood-brain barrier. Bilirubin displacement can cause CNS damage in neonates [21]. The renal and hepatic clearance mechanisms rapidly develop in this pediatric subgroup, requiring continuous evaluation and modification of drug concentrations and efficacy. Drug distribution volumes in young pediatric patients may vary greatly due to their higher surface area to weight, body water, and fat content. Water-soluble medicines dissolve in neonates to a larger extent, potentially requiring a higher dose to achieve the required plasma concentration. Oral absorption is difficult to predict in this class of infants due to higher gastric pH and increased absorption of acid-labile drugs.

8.3. Toddlers and infants.

Infants grow and mature rapidly, with significant intrasubject variability due to individual differences in organ maturation rates and physical growth. As children reach 23 months old, oral absorption improves significantly, and gastric pH reaches adult levels [22]. Clearance mechanisms mature quickly, with clearance often surpassing adults due to the liver being up to 50% larger in children. Hepatically cleared pharmaceutical dosages may need to be increased.

8.4. Children.

Children have similar clearance pathways as adults but often surpass levels in adults due to the maturation of metabolic processes. The surface area-to-weight ratio is higher in neonates and young children than in adults, increasing the risk of severe systemic exposure and associated side effects with topical drug delivery [23]. Research on this subgroup focuses on the effect of drugs on growth and development, as children carrying out academic activities may experience difficulties with their psychomotor abilities and efficacy endpoints when taking CNS-active drugs. Puberty can affect the efficacy of metabolizing enzymes, necessitating significant changes in the dose of drugs like theophylline. Studying the effect of puberty on medical products and biological markers can indirectly evaluate the drug's effect.

8.5. Adolescents.

Adolescents need to assess the impact of dosage forms on their physical, mental, and sexual development, as hormonal changes are significant in this age group. Hormonal shifts can affect the frequency and severity of several illness states, such as asthma and migraines [24]. Biopharmaceutical differences between adults and children can affect a drug's absorption, distribution, metabolism, and excretion (ADME) and the needed dose [25]. Therefore, the patient's age and pharmacokinetics must be considered when developing a dosage form for pediatrics.

9. Formulation Related Challenges

The formulation-related challenges in developing medicines for full-term newborns include dosage form selection, dosing accuracy and flexibility, excipient selection and safety, palatability and patient compliance, regulatory and clinical trial challenges, and extemporaneous compounding. Tablets and capsules are typically unsuitable for newborns and infants under 4 years old, and alternative buccal dosage forms like lozenges, gummies, and chewing gums may be more appropriate. Dosing accuracy and flexibility are crucial for ensuring precise dosing based on the new-born's age, weight, and body surface area to reduce medication errors. Controlling excipient impurities is also essential as they can have severe consequences for new-borns. Palatability and patient compliance are essential for improving acceptance and adherence, as new-borns have a more sensitive sense of taste.

Regulatory and clinical trial challenges include addressing regulatory requirements for developing age-appropriate formulations for new-borns and conducting clinical trials in the new-born population, which can be problematic due to small patient numbers. Extemporaneous compounding is necessary when commercial products are unavailable and lacks stability and consistent data. Most medications are prepared in the form of solid oral dosage forms, typically tablets and capsules (NF-14). However, a substantial percentage of pediatric and geriatric populations face problems in swallowing these dosage forms (dysphagia). To overcome this challenge, oral dispersible tablets, oral dispersible films, mini tablets, and chewable tablets are developed. In the initial stages of the development of novel pharmaceuticals intended for oral administration, the property of a compound is seen for its suitability for an adult dosage form. It has become important to check the compatibility and toxicity of the excipients that are to be used in the formulation and formulate a 'child-friendly dosage form' after the unfortunate 'Diethylene glycol poisoning' incident [26].

Liquid dosage forms have some limitations, such as including excipients to enhance the solubility of active ingredients, preservatives, and surfactants, which may be harmful to children. Non-uniform dosing and stability maintenance can be a problem in liquid formulations, and they tend to be more expensive than oral solid dosage forms and less accessible to the less economically developed class.

One of the most significant formulation issues with major drug substances is undesirable palatability. Flavoring agents, sweetening agents, amino acids, coating agents, and polymeric materials have all been used to address this issue. However, doing taste studies on healthy children may raise ethical concerns. The European Ad hoc committee on ethical concerns of clinical studies in minors states that healthy children should not be registered as healthy volunteers because they cannot give their consent and are vulnerable in the same way that children with illnesses or disorders are. An exception might be made for healthy kids who take part in palatability tests, such as swill and spit taste tests for new flavors of drugs. When given to kids with an ailment that must be treated, the taste should be assessed, and the study will be incorporated into another clinical trial. Taste can be evaluated during successive doses contrary to studies carried out on single administration in volunteers.

10. Toxicity of Excipients in Pediatric Dosage Form

The toxicity of excipients in pediatric dosage forms is a critical consideration in developing pediatric dosage forms. Commonly used excipients in adult formulations can be potentially toxic or problematic for pediatric patients, especially neonates and young children.

These include propylene glycol, ethanol, benzyl alcohol, parabens, and lanolin. Propylene glycol toxicity has been reported in new-borns and children, leading to hyperosmolarity, metabolic acidosis, and other adverse effects [27]. The EMA has set safety thresholds for propylene glycol exposure in pediatric formulations, which can cause neurological toxicity. Ethanol exposure in pediatric formulations can also cause neurological toxicity. Parabens used as antimicrobial preservatives have an acceptable daily intake limit set by the EMA, but these limits are not specific to pediatric populations. The selection of excipients for pediatric formulations requires careful consideration of their safety and suitability for the target age group, considering differences in absorption, metabolism, and elimination compared to adults. In some cases, unique pediatric formulations may require the use of excipients with little or no human use data, necessitating toxicology studies in juvenile animal models to establish safe exposures.

11. Clinical Trials for Oral Solid Dosage Forms for Pediatric Patients

Clinical trials for oral solid dosage forms for pediatric patients should be publicly registered to safeguard participants from pointless or redundant experiments, increase transparency, and prevent publication bias and selective outcome reporting. Regulatory agencies, ethics committees, and journals strongly support prospective trial registration as a requirement for publishing. However, examining available pediatric randomized controlled trials revealed that several had insufficient and poorly reported data on adverse medication reactions. Public trust and confidence in pediatric research are increased when unbiased results, even negative ones, are promptly and openly published. Clinical trials in pediatric patients can be challenging due to the lack of pediatric patients with the same medical issue as under study. It isn't easy to convince parents to allow their children to be part of clinical studies. Additionally, performing clinical trials for a novel formulation developed by pharmaceutical industries for children, with modified release profiles, may contain certain excipients unsuitable for children of a particular age group. Finding a balance between the necessity of conducting trials to safeguard children from the risk of ingesting untested medications and the need to protect them from unknown risks and damages that may arise by participating in trials is challenging. The same moral standards apply to adult cases: respect for persons, beneficence, non-maleficence, and justice apply to cases involving minors. The inability of children to comprehend the hazards associated with trials and dependence on adults to make decisions for them present extra ethical issues. As such, while solid oral dosage forms can be a viable option for pediatric patients, the clinical development of these formulations faces unique challenges that require thoughtful planning and execution to ensure their safety, efficacy, and acceptability.

12. Expert Opinion

The pharmaceutical industry is increasingly focusing on expanding the range of age-appropriate drugs, as pediatric patients are considered therapeutic orphans due to their unmet therapeutic needs. The enforcement of new guidelines for developing pediatric formulations, advances in oral solid dosage forms, improved clinical trials, and an increase in patents for flexible dosage forms. Regulatory bodies have encouraged applicants to work on new dosage forms, devices for administration, and packaging to improve patient acceptance, reduce dosing errors, and increase drug solubility and permeability. Liquid oral dosage forms for children

have slipped several spots in the hierarchy of preferred formulations due to stability, solubility, storage, and transportation issues. Patents show an increase in flexible dosage forms, and mini tablets are well-accepted by children but require dosing devices for accurate dosing. Other taste-masking techniques, such as coating with a polymer and adjusting the pH of the pharmaceutical formulation, have been used to mask the unpleasant taste of medications [28].

The STEP database was developed through a collaboration between the European Pediatric Formulation Initiative and the United States Formulation Initiative to provide information on the safety and toxicity of excipients [29]. A smooth transition to formulations devoid of preservatives could be supported by replacing multidose liquid formulations with single-dose solid dosage forms. Despite about a decade of legislation and guidelines, information about pediatric dosage forms remains limited due to limited evidence on clinical trial methodologies and ethical restrictions for under-aged participants. However, a 2.5-fold increase in pediatric clinical trials from 2007 is an admirable step in the right direction [30].

In the future, the pharmaceutical sector will adapt and overcome challenges in new drug development, leading to a quantifiable expansion of the age-specific market. There is a noticeable increase in research projects and funding opportunities for the development of formulations suitable for pediatrics, and the development of pediatric research networks aims to encourage cooperation between regulatory bodies, academic institutions, industry, patient associations, and healthcare providers to share knowledge and comply with regulatory agency requirements.

13. *In vitro* Models

Surrogate *in vitro* drug dissolution assessment is a method used to evaluate the taste acceptance of a medicinal product by measuring the percentage of drug load released at specified time points from a formulation into simulated saliva. This method is simple, cost-effective, and convenient. Still, it does not provide the threshold concentration for bitterness detection in the target population, consider the size of the drug load in the formulation, or account for variations in bitterness intensity between drugs or the role of excipients in modulating the organoleptic properties of the formulation. There is no published consensus on the methodology for sampling time points, type, volume, and agitation of the simulated saliva dissolution medium for *in vitro* drug dissolution studies to generate reliable surrogate taste scores. E-tongue technology employs a range of flavor sensors to detect the five basic tastes: bitterness, sweetness, saltiness, sourness, and umami [31]. However, it lacks the capacity to identify non-ionizable drugs in the sample medium and is limited to evaluating solutions. *In vitro* drug dissolution experiments are conducted for formulations, not solutions, and the e-tongue is employed to analyze the drug released from the formulation into the dissolution medium.

Bioactive electronic tongues (BioETs) have advanced in recent years, providing high sensitivity and specificity to the taste of various medium and long-chain fatty acids [32]. However, in-depth knowledge of receptor cells that specialize in detecting distinct tastes or textures is crucial for determining overall taste acceptability using BioETs, which is yet to be validated against human gustatory data.

14. *In vivo* Animal Models

The rodent-based brief-access taste aversion (BATA) assay is a novel method for evaluating the palatability of APIs. It uses a lickometer to measure the frequency of licks made by mildly water-deprived rodents when presented with API tastant solutions at varying concentrations. This method generates a comprehensive concentration-response curve within a short timeframe and with minimal animal usage. However, ethical concerns arise as rodents cannot expel aversive tastants, and experiments are conducted under highly controlled environments. Rodents are also prone to heightened sensitivity to bitterness tastes, which may not allow for direct data translation [33]. Ethical approvals may also prolong product development timelines. Fish or flies have been used to evaluate the deterring effects of tastants, but there is no published method for taste evaluation of medicinal formulations using these animal models [34]. Taste scores generated using animal models must be translated to provide equivalent human data, making correlating an animal's aversive response to human taste data difficult.

15. Human Taste Panel

Human taste panels are considered the gold standard for evaluating taste in products designed for humans. They should be used as a reference point for evaluating taste at various stages of pediatric formulation development, including product creation and clinical trials. However, establishing an appropriate human taste panel for all stages of development has not been widely discussed within the pharmaceutical science community. Consensus-driven human taste panel data will be crucial in the future, as the current process of developing an effective taste-masked formulation for an unpalatable API is inefficient and primarily relies on trial-and-error methods. An approach using artificial intelligence (ANN) algorithms could significantly improve cost efficiency. Human taste panels involved in evaluating pediatric formulations should use a unified scoring system agreed upon by the pharmaceutical industry.

The ideal taste panelist for pediatric formulations would be a child. Still, there are several practical and ethical issues that make it challenging to enroll children for taste trials of medicines. These include higher levels of responsibility in areas like confidentiality, legal consent, absolute risk assessment, and stricter ethical codes of conduct. It is also more difficult to recruit adequate numbers of pediatric participants, and involvement in trials with unpleasant stimuli can be distressing for young patients and their parents. When young children (<5 years old) are the target group, instructions for the taste evaluation procedure can be challenging to convey, and compliance with these instructions may be suboptimal. Evaluating novel APIs presents further difficulties, as safety data may not yet be fully available, leading clinicians to be hesitant to be involved while parents are reluctant to provide consent. Nonetheless, if the continuous evaluation of taste during the medicinal product development phase is crucial, feedback from the relevant population is indispensable in determining acceptable taste profiles. The quality by design (QbD) approach can only be accomplished through the incorporation of validated taste evaluation protocols in the design of experiments (DoE) [35].

Young adult panelists capable of providing independent consent may be a practical alternative to circumvent the ethical barriers associated with using child panelists for the taste evaluation of medicinal products. However, the correlation between adult and child gustatory experiences remains debatable, with concern centering around taste perception, particularly aversion to bitterness taste, which is significantly different between young children and adults. The perception that sensitivity to bitterness in children only becomes comparable to that of adults during mid-adolescence has not been verified.

In the field of sensory evaluation, normative values for gustatory sensitivity have been established for both adults and, more recently, children. The data were obtained using "Taste Strips," a validated gustatory test for four taste endpoints: sweet, sour, salty, and bitter. Comparisons of the datasets in the two studies indicate that the human taste function reaches maturity around 10 years, with maturity occurring slightly faster in girls. In children aged 6-15 years, taste scores for sweet, salty, and bitter flavors and the total taste score increased with age. Conversely, in adults aged 18-87, the taste function decreased with advancing age above 40. This suggests that adults under 40 years have similar taste discrimination scores to children aged between 10 and 15 years, and they may have a more refined ability to distinguish tastes compared to children younger than 10 years old.

Recruiting adults aged 18-40 years as taste panelists could provide a practical solution to providing ongoing taste assessment of pediatric formulations during the development phase. While conventional sensory panels comprising experts who are highly trained in providing detailed taste descriptions may not be necessary for pediatric formulation development, trained assessors outperform consumers due to their familiarity with experimental procedures used for sample evaluation and ability to articulate their taste perceptions. Recent research has shown that even brief familiarization can help enhance consumer performance in analytical taste tests. Identifying and addressing the challenges encountered by taste panelists is also helpful. During the DoE developmental stage, where multiple formulation samples can be prepared, panelists may have to taste a multitude of samples in a single day, which can lead to sensory fatigue and uncertainty when comparing samples that were presented early in the session with those presented at the end of the session.

Emotional factors can impact the results of taste evaluation, but standard reference samples can provide similar baselines for different taste sessions. A known concentration of quinine solution can serve as a reference product. Another obstacle in discriminatory taste evaluation is the persistence of an aftertaste, which is not uncommon among bitter APIs. Water and plain crackers are often offered to taste panelists to neutralize residual tastes, but this approach is not effective for APIs that leave a lingering taste for several hours. There is a pressing need for suitable interventions for taste evaluation of formulations with APIs that leave a prolonged lingering residual taste. A unified taste scoring system in pediatric medicinal formulations is needed, as scores or scales are commonly used to rate the taste of oral medicinal formulations. Most studies employ numeric systems, and some employ categorical scoring methods, but interpreting these scales can be inconsistent, making inter-study comparisons difficult.

One taste-scoring system for evaluating oral medicinal formulations is the visual analog scale (VAS), which has a 10 cm scale with 10 score points, divided into four categories: “excellent” (scores of 0–2), “good” (3–5), “acceptable” (6–8), and “poor” (>8) [36]. Other scoring systems vary in complexity, measurement scales, and target populations. The acceptability of a medicinal product is a complex concept that is not likely quantifiable by a single taste score. Factors such as pain, difficult relationships with caregivers, and the individual’s anxiety can adversely influence their taste score, leading to poor taste scores and requests for another trial tablet. Some studies have attempted to address this by employing a questionnaire that covers multiple aspects contributing to palatability rather than a single parameter of measure. However, this still does not address the interpretation of acceptability. The concept of “the one number you need to grow” (net promoter score) was introduced in 2003 by Reichheld, who suggested that companies can bypass complex and ambiguous

satisfaction measures by simply asking customers if they would recommend the company to a friend or colleague [37]. Companies with exceptional loyalty will achieve net promoter scores ranging from 75% to over 80%.

However, the net promoter score has yet to be applied to assess medicinal products' palatability and therapeutic compliance. Instead, straightforward queries such as “How probable is it that you would recommend this medicine for your child or others?” or “How likely would you be to take this medicine if you were ill?” combined with a data analysis method that consolidates rejection, indecisiveness, and acceptance into a single score could provide a more accurate and persuasive representation of medication acceptance in the pharmaceutical field.

16. Optimising Taste Masking with Artificial Neural Networks

The Quantitative Biochemical Design (QbD) approach to medicinal product development has made the DoE a popular tool for pharmaceutical scientists. However, the DoE relies on mathematical modeling and may not be as powerful as artificial neural networks (ANNs), machine-learning approaches inspired by the human brain. ANNs can model a large number of variables and establish intricate relationships between dependent and independent variables, managing multiple outputs and modeling unstructured data. In the field of pharmaceutical development, ANNs have been employed to predict responses such as dissolution and optimize process parameters. Still, they have not yet been used to predict optimized formulation designs for unpalatable APIs. The initial design of a taste-masked pediatric formulation still largely depends on trial and error, supported by published literature, researcher expertise, and previous experiences. Consumer feedback becomes an increasingly significant component of this research process. Selecting a taste-masking formulation is complex, and no universal technology works for all APIs. There are numerous methods for masking the bitterness of APIs, including adding agents to mask taste, physical barrier methods, and chemical methods. The chosen method depends on multiple factors, such as the bitterness threshold concentration of the API, API–excipient interactions, physicochemical properties of the API, API dose to be administered, and the API load released from the formulation into the oral cavity.

The diversity of bitter molecules makes it challenging to predict whether a compound will taste bitter based on its chemical structure. However, researchers have developed machine learning classifiers to resolve this, such as BitterDB, BitterPredict, BitterIntense, and VirtualTaste [38]. These databases are designed to predict the taste, particularly the bitterness, of individual compounds but do not provide protocols for assessing complex mixtures of excipients and APIs typically present in medicinal formulations.

Advancements in knowledge and machine learning technologies over the past decade may make it possible for researchers to use machine learning to identify patterns in the relationship between molecules and effective taste-masking technologies. Machine learning can integrate numerous variables and uncover hidden correlations that contribute to specific taste experiences and may become proficient at discerning bitterness and its intensity in complex medicinal formulations. A critical requirement lies in having a dataset for the most effective technique for masking the bitterness of specific molecules.

17. Pediatric Drug Development: The Paradigm is Shifting

The development of pediatric dosage forms and drug formulations (Figure 5) has faced significant challenges, particularly in the off-label prescription of adult medications to pediatric patients. However, the paradigm seems to be shifting, and overdue attention has been invested in overcoming the scarcity of pediatric age-appropriate medicines. The regulatory landscape of pediatric medicines was rocked by the "Drug Efficacy Study Implementation Program" conducted between 1938 and 1962, which highlighted the need to reframe the clinical and pharmaceutical pipeline for drug approval [39]. Since the US FDA and the American Academy of Pediatrics (AAP) released recommendations on clinical research in pediatric populations in 1977, the number of children enrolled in clinical studies has been gradually rising [40]. In the US and the EU, pediatric regulations increased in 2007 and provided commercial exclusivity incentives to stimulate the development of pediatric drugs [41]. China has been implementing regulations that support the research and distribution of pediatric drugs since 2011 [42].

Figure 5. Pharmaceutical pipeline and clinical trials timeline.

The Orphan Drug Act and supportive initiatives such as the Pediatric Research Equity Act (PREA), the Best Pharmaceuticals for Children Act (BPCA), and/or the Pediatric Investigation Plan (PIP) have provided a carrot-and-stick approach to pediatric medicine advancements [43]. However, significant heterogeneity in funding sources, pediatric clinical conditions, and study characteristics still impact the participation of the pediatric population in clinical trials.

Among 462,303 registered clinical trials, only 90,920 were designed for children (from birth to 17 years old). Additionally, from the 43,644 clinical trials reported, only 7229 were conducted in the population under 18 years old [44]. Issues regarding age-appropriate equipment and medical techniques, a "child-friendly" environment, pediatric expert physicians and other health professionals, and the management of caregivers may also contribute to limiting the enrolment of the pediatric population in clinical trials. Pediatricians continue to demand more safe medications, especially in the field of molecular target antineoplastic drugs. A recent report revealed that, of 103 drugs approved for adult patients, only 19 were approved for pediatric patients [45].

Additionally, pediatric labeling was not established for 78 medications out of 189 products under pediatric exclusivity (1998–2012), corresponding to a failure rate of 42% [46]. The off-label prescription seems to persist as a rule in pediatrics, with 38.1% of medications prescribed to pediatric patients remaining off-label. The prevalence of pediatric off-label drug prescriptions ranges from 2.7 to 51.2% in outpatients and 9.0 to 79.0% in inpatients [47]. Recent data/evidence presented in Clinical Practice Guidelines could help mitigate the risk of irrational pharmaceutical use and the liability associated with off-label use of drugs.

Age-related effects on drug PK and PD profiles are not fully understood, with PD being the effect of a drug on the body and PK being the effect of the body on a drug. Rapid growth and development during childhood exacerbate dosing issues, with dosages of specific formulations fluctuating 100-fold. The relationship between drug exposure and PD endpoints seems to be weakly studied in children. The FDA has proposed a guideline entitled "General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products" to address clinical pharmacology considerations of any planned pediatric study, whether or not it is conducted under BPCA or PREA. PK parameters are particularly articulated with the measurement of area under the curve (AUC), maximum concentration (Cmax), clearance, half-life, and volume of diffusion (Vd), which in turn reflect the absorption, distribution, metabolism, and excretion (ADME). These parameters tend to differ across different age groups, with relevant emphasis on the pediatric population. Understanding ADME differences may contribute to ensuring effective and safe therapies in pediatric populations. PK measures may consider growth parameters such as age, weight, or body surface area (BSA).

Children's oral absorption, drug distribution, metabolism, bioavailability, and elimination of drugs can be impacted by changes in the pediatric population, including gastric acidity, rates of gastric and intestinal emptying, the surface area of the absorption site, gastrointestinal drug-metabolizing enzyme systems and permeability, biliary function, and transporter expression. Changes in gastric pH, water content, and degrees of vascularization can also affect drug absorption. The ontogeny of drug metabolism in new-borns, infants, and children has been recently included in modeling approaches to predict drug elimination in these groups. The microbiota can also impact drug metabolism in pediatric subgroups compared to adults.

The excretion/elimination (E) of unchanged parent drugs can occur predominantly via the kidneys, through glomerular filtration, tubular secretion, and reabsorption, and can be affected across different pediatric ages. In infants, inadequate levels of bile salt in the ileum may determine the reduced absorption of fat-soluble vitamins, leading to the need for dose adjustments when administering fat-soluble substances for this age group. After a few months, bile salt's postnatal maturation may allow infants to absorb fat-soluble compounds efficiently.

Selecting the most appropriate dosage form for pediatric medications is a complex task with no one-size-fits-all approach. There are various routes of drug administration for pediatric patients, including oral, dermal-transdermal, rectal, intramuscular, parenteral, intrapulmonary, and inhalation. The quantity of the active ingredient (API) modified to the child's age requirements, the dosage form's acceptability, the API's palatability, the minimum dose frequency, end-user demands, and regional and cultural variations should all be considered when designing the optimal dosage form. Pediatrics has made extensive use of oral dosage forms, which include liquid and solid formulations such as solutions, suspensions, elixirs, and syrups, as well as solid dosage forms such as chewable tablets, capsules, orodispersible formulations, powders for reconstitution, and tablets. On the other hand, solid dosage forms provide benefits, including long-term stability, flexibility in manufacturing, cheap production costs, baby acceptance, and suitability for kids and teenagers in school.

Liquid dosage forms are the most commonly used in ages lower than 5 years old due to the facility for swallowing and dose adjustment. However, many of these forms are not labeled for pediatric populations, and those labeled are not available in the appropriate dosage forms. To overcome these issues, some dosage forms, such as tablets or capsules, are used to prepare

"especially" or "extemporaneous" liquid or powder dosage forms. However, this may lead to dosing errors due to poor division or an extemporaneous way of dispensing, which is even more critical for antibiotics widely prescribed to the pediatric population. Dosing volume is also of significant importance when determining acceptability. Target volumes are ≤5 mL and ≤10 mL for children under 5 years and ≤10 mL for children above the age of 5 years, respectively [48]. However, maximum volumes of 5 mL or 10 mL were recommended for children under 4 years or between 4 and 12 years, respectively.

The parenteral route is used in pediatric ages, particularly in acute situations, to ensure a rapid onset of action and high bioavailability in treatment. However, this type of administration requires trained professionals and is a more invasive process with risks of blood-borne infections, injury, and pain induced by injections. Buccal medication delivery is an appealing administration route for pediatric pain management, but physiological considerations, regulatory expectations, and formulation development considerations have limited its broad translation.

Pharmaceutical dosage forms intended for dermal (or cutaneous) administration are tailored to promote a local effect. Transdermal drug delivery in children can be liquid, semi-solid, or solid preparations. Assessing excipient safety is of utmost importance, and ethanol should be avoided as an excipient in preparations intended for very young children. Transdermal patches are used for the systemic delivery of APIs capable of diffusion through the stratum corneum, and although not appropriate for all drugs, various transdermal patches containing different APIs have been applied to pediatric patients. The administration of pneumonia medicines by inhalation has traditionally been used to obtain a local effect and presents the potential for systemic delivery. Inhalation products are mostly used to treat asthma and Chronic Obstructive Pulmonary Disease (COPD) in pediatric patients. Despite progress in drug formulation for the pediatric population, some problems remain to be solved. The design of pediatric drug formulation needs to be based on the patient-centric drug product design process (PCDPD), ensuring that the safety of excipients used in pediatric pharmacotherapy is crucial.

17.1. Nanomedicine for pediatric healthcare.

Nano medicine, a combination of nanotechnology and medicine, is a rapidly evolving field that aims to improve healthcare by exploiting unique bio and physicochemical properties of materials at the nano scale. It involves the application of nano-sized components with specific advantageous properties, such as better targeting and bioavailability of therapeutics, new modes of therapeutic action, and nanostructured surfaces/scaffolds for engineered tissues (Figure 6). In pediatric medicine, nano medicine offers innovative solutions for diagnosing and treating various conditions, particularly cancer, infection, dentistry, dermatology, and nutrition.

Key benefits of nano medicine include improved drug delivery and targeting, enhanced disease diagnosis, crossing biological barriers, and tissue engineering. Nanoparticles, nanocapsules, and nanotubes can more effectively deliver drugs to target tissues, improving efficacy and reducing toxicity in pediatric patients. They can also overcome biological barriers, enabling better treatment of conditions like brain tumors and traumatic brain injury in pediatric patients. However, the use of nanoparticles also carries inherent risks, including potential toxicity. Ongoing research and development in nano pediatrics aim to harness the benefits while addressing safety concerns. Overall, nano medicine represents a paradigm shift in

pediatric healthcare, moving away from treating children as "therapeutic orphans" and enabling more personalized, effective, and safe treatments.

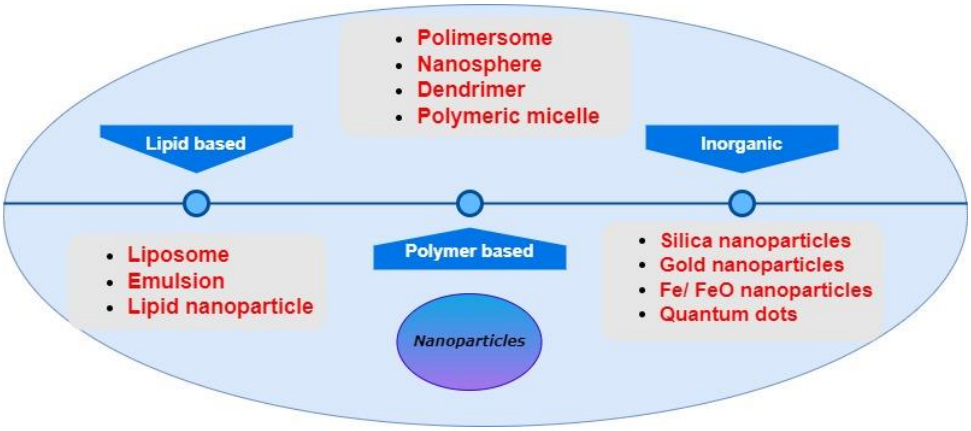

Figure 6. Different types of nanoparticles can be used in nano medicine.

17.2. Lipid-based nanoparticles.

Lipid-based nanoparticles, including liposomes, lipid nanoparticles, and emulsions, are highly approved nano medicines by the FDA due to their advantages, such as biocompatibility, formulation simplicity, and payload flexibility. Liposomes are composed of phospholipids and can form unilamellar and multilamellar vesicular structures, allowing the delivery of hydrophilic, hydrophobic, and lipophilic drugs in the same system. Nano-emulsions are heterogeneous oil-in-water or water-in-oil emulsions formed by oil droplets containing the API, stabilized by surfactants and cosurfactants, and dispersed in an aqueous external phase. They are usually prepared using Generally Recognized as Safe (GRAS)-grade excipients approved by the FDA. Next-generation lipid nanoparticles, such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), have emerged to overcome the limitations of conventional lipid-based nanosystems. These nanoparticles can offer targeted drug delivery, increase hydrophobic drug bioavailability, and protect sensitive active compounds. Lipid-based nanoparticles have been widely investigated for various applications, including cancer and COVID-19 vaccine formulations. Liposomes are the most widely studied in pediatrics, with transversal variations in PK parameters registered between adult and pediatric populations.

Other types of lipid nanoparticles, such as *in situ* self-assembly nanoparticles (ISNPs), have been investigated, such as child-friendly Lopinavir/Ritonavir pediatric granules and nano-assemblies using squalene-gemcitabine and alkyl-lysophospholipid edelfosine [49]. These nanoparticles have shown high uptake by human osteosarcoma cells, resulting in antitumoral activity and enhanced pharmacokinetic profiles.

17.3. Polymer-based nanoparticles.

Natural (Figure 7), semi-synthetic, or synthetic polymers (Figure 8) can be combined to create polymer-based nanoparticles, which provide a vast range of potential topologies and properties. These have a variety of therapeutic uses and include dendrimers, polymeric micelles, polymersomes, nanospheres, and nanogels. Natural polymers can be either biodegradable or non-biodegradable, and they usually have less harmful consequences than manufactured polymers. Biodegradable polymers can break down enzymatically or non-enzymatically *in vivo*, producing harmless or biocompatible byproducts. Biodegradable

polymers encompass a variety of polysaccharides, such as alginate, chitosan, hyaluronic acid (HA), and dextrin. A naturally occurring cationic polymer with minimal toxicity that is biocompatible and biodegradable, chitosan is derived from deacetylated chitin that is sourced from fungus, insects, squib centric diatoms, and crustaceans. The FDA has authorized it as a biomaterial for tissue engineering and medication delivery applications, categorized as GRAS. Because HA is non-immunogenic, biodegradable, and biocompatible, it can be used in nanomedicine applications. Hyaluronic acid (HA) is a mucopolysaccharide that is found in connective tissues, synovial fluid, and extracellular matrix. It is composed of alternating units of 1-b-3 N-acetyl-D-glucosamine and D-glucuronic acid. Due to its viscoelastic nature and biocompatibility, non-immunogenicity, and biodegradability, HA is a good fit for uses in nanomedicine. The primary HA receptor, a cluster of differentiation-44 (CD44), is overexpressed in solid tumors, which makes it a good candidate for cancer targeting [50]. In order to improve patient compliance, HA has been researched for pediatric medication formulations. This has involved changing the dosage form or reducing the frequency of doses.

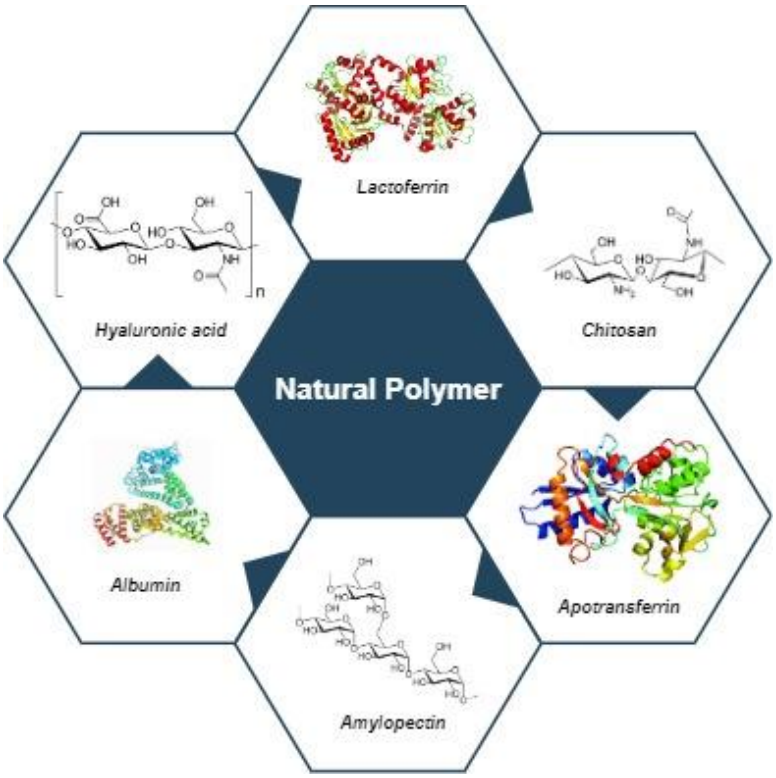

Figure 7. Representation of some natural polymers.

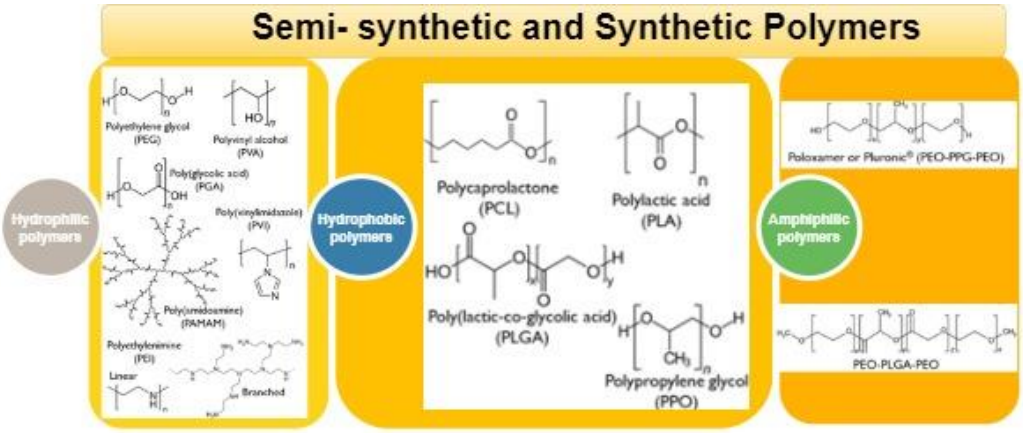

Figure 8. Representation of some semi-synthetic and synthetic polymers.

Protein-based biomaterials, such as albumin, lactoferrin, or apotransferrin, are another class of natural polymers. Since its hemocompatibility, albumin- a globular protein soluble in water and makes up over 50% of plasma body mass- has been used in intravenous medication and gene administration. The FDA approved an albumin-based nanosystem 2005 to administer paclitaxel (Abraxane®) [51]. Nevertheless, Abraxane®'s efficacy and safety in pediatric patients have not yet been determined. A naturally occurring cationic iron-binding glycoprotein found in milk, lactoferrin (LF) has immune-stimulating, antiviral, anti-inflammatory, and antioxidant properties. Since LF receptors are known to be overexpressed in endothelial brain cells and cancer, they can be used for brain delivery by receptor-mediated transcytosis across the blood-brain barrier (BBB) or for active tumor targeting. Commercial bovine lactoferrin preparations, which the FDA has classified as GRAS, are often utilized in both *in vitro* and *in vivo* experiments. Pediatric applications have also made use of synthetic or semi-synthetic polymers. Due to its biocompatibility and biodegradability, the FDA-approved synthetic polymer PEG is widely utilized. Since it enhances the pharmacological qualities of nano medicines and offers stealth qualities, it is frequently paired with other, more hydrophobic polymers or other API nano carriers. Due to its high drug permeability, polycaprolactone (PCL) is considered non-toxic and appropriate for controlled/sustained medication and vaccine administration. With better circulation time and permeability, the FDA-approved polymer polylactic-co-glycolic acid (PLGA) has demonstrated appropriate qualities for drug administration. Due to their special qualities for gene transport, other synthetic polymers like polyethyleneimine (PEI), poly(vinylimidazole) (PVI), or poly(amidoamine) (PAMAM) will be covered in greater depth. Owing to their adaptability, various polymer arrangements can produce distinct nanoparticle structures.

17.4. Polymeric micelles.

Since amphiphilic block copolymers self-assemble in an aqueous solution to form core-shell structures, polymeric micelles are adaptable drug carriers and active ingredients. The use of amphiphilic-block co-polymers, such as Pluronic® and Tetronic® surfactants, which produce polymeric micelles above critical micellar concentration/temperature with single features, provide flexibility for functionalization. Curcumin was included using Pluronic® mixed micelles based on the F127 and P123 surfactants to treat pediatric osteosarcoma. A few polymeric micelle-based nanomedicines, including Genexol-PM®, Nanoxel-PMTM, and Paclical®, are already available for purchase. In South Korea, the Philippines, India, and Vietnam, the polymeric paclitaxel formulation Genexol-PM® is authorized for the treatment of ovarian cancer, metastatic breast cancer, and non-small cell lung cancer. The Indian Drug Controller General has authorized the micellar formulation NanoxelTM, which contains paclitaxel as the active ingredient, since 2006 [52]. In November 2018, the EMA authorized the commercial use of Paclical®, a paclitaxel formulation devoid of CremophorEL and based on XR17 micelle platform technology, for treating ovarian cancer in female patients [53].

17.5. Dendrimers.

Hyperbranched three-dimensional polymeric nanostructures known as dendrimers are surfaces and cavities that contain functional moieties. For medication delivery applications, they are referred to as "smart carriers" because of their capacity to release their payloads in certain settings, minimizing adverse effects. As their oral dose forms cause unpleasant

feedback and nausea, dendrimers can be used as a replacement administration mode for transdermal drug delivery. When dendrimer absorption in rabbits was examined 24 hours after intravenous injection, it was found that over 90% of the administered dose had been cleared out and that less than 5% of the amount was still in the bloodstream. Four nm-sized G4-OH dendrimers were predicted to exit the body through the kidney. Ruthenium-terminated carbosilane dendrimers severely reduced the vitality of juvenile leukemia cells, but non-cancer cells showed no damage [54].

17.6. Inorganic nanoparticles.

Atherosclerosis and cancer are two common uses for inorganic nanoparticles, such as metal, rare-earth, and silica nanoparticles. Certain inorganic nanoparticles have received FDA approval for use in anemia treatments and iron replacement therapy. Pediatric therapies are being examined using Venofer® and Ferrlecit®. Venofer® is an iron oxide nanoparticle coated with sucrose for gradual iron breakdown after intravenous administration. A stable combination of sodium ferric gluconate in sucrose is called Ferrlecit®. The potential use of inorganic nanoparticles in the detection, management, and surveillance of pediatric brain tumors and other diseases has been brought to light by research in this area. Angiopep-2-PEG-doxorubicin-gold nanoparticles are a hybrid nanoparticles with promising properties, including the capacity to target glioma cells and cross the blood-brain barrier.

18. Challenges in Using Nano Therapy in Pediatrics

Due to information gaps and the preferred route of administration for pediatrics, there are obstacles (Figure 9) in the way of applying nanotechnology in medicine. These issues are especially present in the pediatric population. Pediatrics prefers p.o. administration, while preclinical investigations frequently evaluate the physicochemical features of nanosystems in adult animals. There may be additional obstacles to assessing the PK parameters of nanoformulations. Since pediatrics is a relatively new field to research, there is much to learn about applying nano therapies. It is crucial to take into account environmental exposure, safety and efficacy, informed consent, public awareness of nanotechnology, and socioeconomic problems while developing a nanomedicine for pediatric use. The benefits and drawbacks of nanomedicine should be considered at every stage of development, with an emphasis on children's welfare and best interests. The European Parliament has termed nanomedicine the "therapies for the future".

Figure 9. Some issues remain in developing nanotherapies for pediatric patients.

19. Advanced Therapy Medicinal Products (ATMPs) for Pediatric Healthcare

Pediatric conditions such as B-cell acute lymphoblastic leukemia, melanoma, lymphoma, spinal muscular atrophy (SMA), and retinal dystrophy can all benefit from the use of Advanced Therapy Medicinal Products (ATMPs). These treatments provide curative alternatives and life-changing advantages and have demonstrated amazing success in pediatric patients. The translation of research into patient access, particularly in pediatric healthcare, is a barrier that the field of ATMPs must overcome. These include tackling scientific and regulatory challenges, guaranteeing reliable production processes, maximizing ATMP performance, and cost justification. Furthermore, when conducting clinical trials involving children, special considerations need to be made for pediatric populations. These particular concerns include long-term follow-up, research population selection, and possible consequences on future transplant success. In order to get the most benefit from ATMPs in terms of bettering the health outcomes of children, it is imperative to tackle issues pertaining to safety, effectiveness, regulatory compliance, and financial viability. ATMPs comprise tissue-engineered products (TEPs), gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (sCTMPs), and combined ATMPs (Figure 10), which may mix tissue or cells with a medical device.

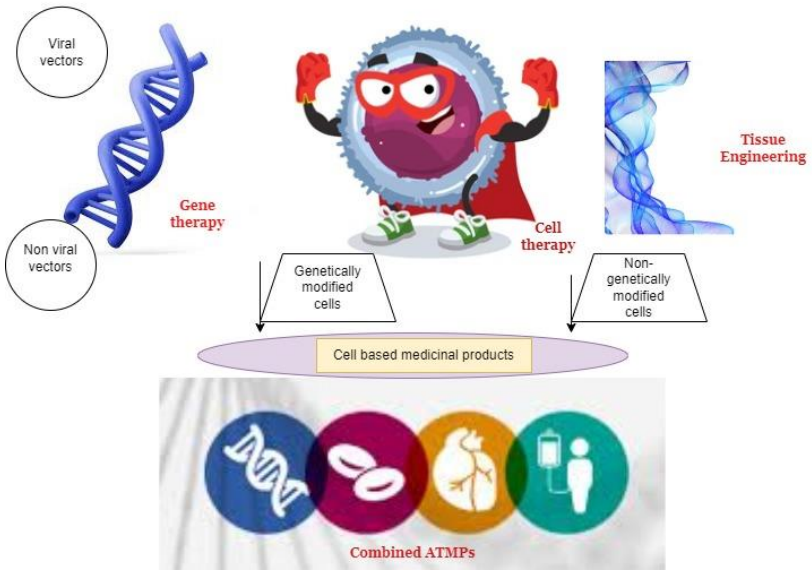

Figure 10. Advanced therapy medicinal products (ATMPs).

19.1. Gene therapy.

Recombinant nucleic acids are used in gene therapy medications to treat, prevent, or cure illnesses. Three primary methodologies can serve as their foundation: ex vivo, *in vivo*, and *in situ*. Ex vivo gene therapy is the process of genetically modifying cells external to the body in order to generate therapeutic factors, which are then transplanted into patients. *In vivo*, gene therapy aims to alter the target cells' genetic repertoire while still alive. Rare genetic abnormalities can now be successfully treated, thanks to the development of safer and more effective viral vectors based on lentiviruses and enhanced technology for the scale manufacture of viral vectors. In 2016, the European Medicines Agency (EMA) authorized Strimvelis, the first ex vivo gene therapy in history, to treat children patients with ADA-SCID (adenosine deaminase deficiency severe combined immunodeficiency) who lacked an appropriate cell donor [55]. During a 7-year follow-up, a single infusion of autologous bone marrow HSC that

had undergone gene correction using γ-retrovirus technology led to the long-term correction of T cell function, immunological reconstitution, and 100% survival. Patients treated with lentiviral (LV) HSC treatment for Wiskott-Aldrich disease, X-linked adrenoleukodystrophy, metachromatic leukodystrophy, or transfusion-dependent β-thalassemia showed comparable clinical improvements. By avoiding the immunologic disparities between the host and recipient and the requirement for significant immune suppression, adopting such autologous therapy also gets around the drawbacks of allogeneic therapies. However, a variety of factors can impact the course of treatment for individual patients or different diseases, and the use of ex vivo therapy is constrained by the high cost, short shelf life of genetically altered cells, and need for highly specialized experts involved in all stages of product production and performance. Long-term surveillance of the dangers associated with insertional mutagenesis, oncogenesis, immunogenicity, and off-target consequences is required in order to realize the therapeutic promise of ex vivo gene therapy fully. To get around issues with viral vectors, non-viral vectors based on cationic lipids or polymers have been investigated. Commercially accessible cationic lipids include N-[1-(2,3-dioleyloxy) propyl] and 1,2-dioleoyl-3-trimethylammoniumpropane (DOTAP). 2-[2(sperminecarboxamido)ethyl]-N, N, N-trimethylammonium chloride (DOTMA), 2,3-dioleyloxy-N-Dimyristyloxypropyl-3-dimethyl-hydroxyethyl ammonium bromide (DMRIE) and N, N-dimethyl-1-propanaminium trifluoroacetate (DOSPA). Cationic liposomes have been a popular choice for gene vectors due to their favorable pharmacokinetic characteristics and minimal immunogenicity.

Polyethyleneimine (PEI), the gold standard for nucleic acid delivery since 1995, is one of the most researched non-viral vectors. PEIs are a class of artificial, water-soluble, linear, or branching polymers with positive charge density at physiological pH that are made up of primary, secondary, and tertiary amine groups. Due to their "proton-sponge" ability, which shields the nucleic acid payload from lysosomal degradation, they are a good fit for gene therapy. There is just one clinical study recruiting at this time to investigate a vaccine based on PEI.

Monodisperse, hyperbranched polymers known as Poly(amidoamine) (PAMAM) have been extensively used for gene transfer. The PAMAM dendrimer's fourth generation has shown promise in transporting drugs, peptides, and DNA. It may be selectively beneficial in some circumstances, such as cancer therapy, when tumor cells have high intracellular negative charges.

Water-soluble poly(vinylimidazole) (PVI) is a polymer that possesses extra biocompatibility qualities, low toxicity, and the capacity to bypass the endosome through the "proton sponge" process. It is also being investigated if PVI may be used in biological applications either by itself or in conjunction with other polymers like poly(acrylamide).

Gene therapy has been transformed by the CRISPR/Cas9 gene-editing technique, which makes it possible to permanently cure harmful base mutations or interfere with the genes that cause diseases. The potential of this technique to treat infectious disorders that affect children, such as malaria, which may be fatal for those under five, has been investigated. Dong et al. described a CRISPR/Cas9-based gene editing method for treating malaria [56]. By focusing on the BCL11A erythroid-specific enhancer, the technique has also been investigated for treating severe monogenic disorders such as sickle cell disease (SCD) and transfusion-dependent β-thalassemia (TDT). Two clinical studies have been carried out to evaluate the safety and effectiveness of autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) in patients with TDT and SCD. In a different study, a CRISPR/Cas9

system was created to fix the COL7A1 gene, which results in the skin and other organs being affected by recessive dystrophic epidermolysis bullosa (RDEB).

19.2. Cell therapy.

Regenerative medicine, immunotherapy, and cancer therapy are all components of the complex field of cell therapy. It combines treatments based on stem cells with non-stem cells, usually with the use of autologous or allogeneic cells. Approximately 17% compound annual growth rate (CAGR) is projected for the worldwide cell treatment market between 2023 and 2030 [57]. While high production costs and possible tumorigenicity raise safety concerns, cell-based medicines have special inherent qualities that may improve treatment efficacy.

Three types of stem cell treatments are available: cancer stem cells (CSCs), adult stem cells (ASCs), and pluripotent stem cells (PSCs). As PSC and ASC-derived organoids may imitate organs *in vitro*, they are a popular issue in translational stem cell research. Clinical trials have employed CSCs to stop the spread and recurrence of cancer. Based on hematopoietic or mesenchymal cells, stem and progenitor cell treatment is authorized for treating a variety of blood malignancies, blood diseases, and tissue regeneration. Since the middle of the 20th century, bone marrow transplants for patients with blood-borne malignancies have been the main focus of human stem cell therapy. Nonetheless, since 2007, 202 clinical trials on pediatric illnesses have been finished; however, most of them were brief, single-center investigations with limited patient enrolment and gender constraints [58].

Non-stem-cell treatments entail extracting somatic cells from the human body, followed by their propagation, expansion, selection, and administration to patients for therapeutic, prophylactic, or diagnostic objectives. These treatments include fibroblasts, chondrocytes, keratinocytes, hepatocytes, pancreatic islet cells, and immune cells such as T cells, DCs, NK cells, or macrophages.

19.3. Tissue-engineered products.

According to EC No. 1394/2007, tissue-engineered goods are made of or include changed cells or tissues. When administered to people, they display properties that allow human tissue to regenerate, repair, or replace it [59]. A tissue or cell is considered engineered if it satisfies one of the following two requirements: it has undergone major modification or is intended to perform a different primary function or function in the recipient than it did in the donor.

19.4. Combined ATMPs.

Medical devices that integrate a GTMP, sCTMP, or TEP with one or more active implantable medical devices (implanted as an integral component of the product) are known as combined ATMPs (cATMPs). They make up just 1% of the ATMPs that the EU is currently developing [60]. Before being sold commercially in the EU, medical equipment must be certified and have the CE label, an acronym for "Conformité Européenne" (European Conformity) in French. Before being sold in the EU, any medical device containing a cATMP needs to have been given the CE mark by the notified organizations. Special release testing can be necessary if a medical device is part of the finished product. Cardiovascular illnesses, ophthalmology, endocrine, nutritional, metabolic, genetic, and hematological malignancies are among the conditions in which cATMPs are very interested. Nevertheless, the EU database

does not yet contain clinical trials using cATMP for neurological applications. Due to the existing shortage of combination ATMP treatments on the market and in clinical trials, there may be a significant research and funding opportunity.

20. Future Perspectives

Although the field of pediatric medication research has changed dramatically in the last several years, a number of problems still need to be resolved. Age-appropriate drug formulations, safety data for excipients used in pediatric drug development, age-adjusted administration routes, complete pharmacokinetic data, low market size, and profitability, lack of approved APIs for the pediatric population, and challenges in creating *in vivo* models that replicate various pediatric subgroups are a few of these. Preclinical and clinical research has shown encouraging results in enhancing the solubility, organoleptic characteristics, therapeutic efficacy, and safety of a wide range of APIs, suggesting that nanomedicine may offer a solution to these problems. A sizable divide must be addressed before the majority of bench-formulated nanomedicines, especially those for pediatric patients, can be brought to patients' bedsides.

With the development of Artificially Transformed Pharmaceuticals (ATMPs), pediatric diseases may now be completely cured. However, concerns about immunogenic side effects and safety still need to be addressed. These novel treatments also pose problems for pharmaceutical companies and healthcare systems, which may be summed up by the "four As": authorization, availability, assessment, and cost. Issues with pharmacovigilance might limit the amount of ATMPs that are currently used in clinical settings. Economic issues brought on by large expenses and little earnings might discourage investment in this field.

Whether pediatric medicine is still a "therapeutic orphan," whether healthcare and economic systems are ready for personalized medicine, and whether governments, regulatory bodies, and society as a whole are ready for the demands that the field of nanomedicine and, in particular, the use of intelligent nanomaterials and ATMPs will place on them are among the many unanswered questions.

21. Conclusion

Pharmaceutical industries have not been the primary focus of developing pediatric dosage forms for years, but recent advances have changed this scenario. The development of pediatric dosage forms can be challenging due to biological factors, physiological development stages, drug properties, taste, and stability. The palatability of oral solid dosage forms significantly affects patient adherence. Implementing the New European Pediatric Regulation has motivated further research on palatability, and smaller market sizes have hindered the growth of pediatric formulations. Regulatory acts have provided guidelines for developing pediatric formulations and conducting clinical trials, promoting safe dosage forms for children, and minimizing exposure to toxicity during trials. Factors such as route of administration, excipients used, and dosage should be tailored to the pediatric population rather than comparing or taking standards from adult dosage forms. Pediatric projects in the U.S. and Europe are two significant programs addressing toxicity issues in pediatric dosage forms. The STEP database was created to provide information about the toxicity, pharmacology, and safety of excipients used in pediatric dosage forms, helping determine the most suitable excipient for a particular dosage form. Clinical trials in children are minimal due to issues related to toxicity, lack of consent, and parental hesitation. Balancing risk-benefit ratios and informed consent can help

formulate age-appropriate, most suitable dosage forms for pediatric patients. The development of flexible dosage forms, such as mini-tablets, chewable tablets, orodispersible films, and tablets, along with modifications in conventional dosage forms, may increase the preference of the pediatric population toward oral solid dosage forms.

The ideal taste panelists for pediatric formulations are children, but due to ethical, practical, and regulatory challenges, young adults are often used as substitutes. Taste sensitivity matures around 10 and declines with age, making adults aged 18-40 more suitable for evaluating pediatric formulations. A unified taste scoring system for pediatric formulations has yet to be established, but adopting a simplified approach could provide a more accurate representation of medication acceptance. A compliance value that the pharmaceutical community can agree upon could lead to a more consistent and effective evaluation system for pediatric formulations. Artificial neural networks (ANNs) offer a comprehensive approach to taste masking optimization, allowing for better prediction and optimization of desired product profiles. Machine learning classifiers can be used to predict bitterness and its intensity in pediatric formulations. Further advancements are needed to identify specific molecules' most effective taste-masking techniques. Researchers can improve pediatric formulation development and overcome taste-masking challenges by using human panelist acceptability scores and continually refining machine learning algorithms.

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Conflicts of Interest

The authors declare no conflict of interest.

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