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A Review of the Safety and Acceptability of Commercially-Available Pediatric Drug Formulations

Cristine Ray Laluna[1] · Denise Marfe Pedregosa[1] · Sophia Mae Abarca[1] · Sophia Loi Camiña[1] · Hannah Faith Lopez[1] · Joseph Mari Querequincia[1]

[1] San Pedro College, Davao City, Philippines

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ABSTRACT

Until now, drug formulations are still among the most important inventions, and ongoing research is being done to enhance their acceptability and efficacy in a variety of patient populations, as shown in both adults and pediatrics. Both age groups differ in a number of ways when it comes to the pharmacological element and therapy, including their aptitude for administering pharmaceuticals, how they respond to negative drug reactions, how they prefer to taste medications, and a host of other factors. Particularly, pediatrics and their pharmaceuticals require top priority due to the fact they must match and coincide with their age, size, physiological needs, and therapeutic requirements. This calls for addressing and elevating variations in these areas, particularly in pharmacokinetics, pharmacodynamics, formulation development, and regulation. This review explored these variations through a list of potentially-harmful medications for pediatrics presented in tables, as well as their uptake in adverse drug reactions than that of adults and pharmacodynamic differences, leading to the utilization of the physiologically-based Pharmacokinetic (PBPK) model for DDI prediction and evaluation model on pediatric-pharmacokinetic DDIs to assist in the safety and acceptability of commercially-available pediatric drug formulations.

Keywords: Pediatrics, Children, Drugs, Drug Formulations, Pharmacokinetics, Pharmacodynamics, Adverse Drug Reactions, Drug-Drug Interactions

Introduction

Pediatric formulations are purposely designed to be delivered to infants and children, specifically formulated for pediatric patients to obtain a desired pharmacokinetic effect. Children and adults have differences in many aspects of pharmacotherapy including the ability to administer drugs, toxicities involving medicines, and preferences in terms of taste. The oral route has been seen to be most conveniently used in administering pediatric formulations, with the relatively reconstitution of the formulation since oral pediatric formulations are given in a powder form. However, these formulations require purified water and unique storage conditions, thus leading to oral pediatric formulations not being able to meet the desired requirements including the safety and efficacy of the medication since they are relatively difficult to develop from a scientific standpoint due to special criteria and limitations [1-2]. Pediatric patients also have differences in terms of physiology and cognitive and motor skills when compared to adults, therefore, it is necessary that these formulations are compatible with the child's age, size, physiologic condition, and treatment requirements [3].

Pediatric patients are identified as patients aged from birth to 18 years old. They are classified according to the pediatric patient's age. However, there is inconsistency when allocating pediatric patients into specific age groups for drug administration, since it might not consider pharmacokinetic parameters, such as renal or hepatic function, volume of distribution, lipophilicity, relative blood volumes, etc. This phenomena is a concern, as pediatric formulations are age-specific or should be administered based on their body weight [4]. This leads to careful consideration of the acceptability of different doses for different age groups, thus, the existence of Pediatric Drug Development.

The term Pediatric Drug Development (PDD) is defined by FDA, EMA, and the American Academy of Pediatrics (AAP) as a separate regulatory approval of medicines for minors as well as separate labels. The fact that children are not a different species, thus not requiring rational pediatric drug use or even labeling on efficacy and safety studies on drugs [5]. In the

past, children were considered to be "small adults", administering the medication dose which was simply scaled down per linear wright, often resulting in overdosing in very small children and neonates due to their kidneys and liver not being fully developed, thus slower drug elimination [6]. Since developmental pharmacology expanded, the physiological differences in drug handling were emphasized between children and adults, concluding the notion that "children are not small adults". In line with this, the development of pediatric dosage forms has always been challenging, and one of the main challenges includes selecting the most appropriate and suitable formulation with regards to patient age [4]. The broad range of pharmaceutical and clinical aspects contribute to the challenging tasks of developing an age-appropriate formulation considering the assurance of quality, safety, and efficacy of the medication [7].

On the other hand, excipients are one of the most important ingredients in drug formulations as it is added to ensure stability, improve palatability, facilitate solubility, and as a preservative; in fact, pediatric formulations contain a broader range of excipients compared to adult forms, which makes it more complex. However, there is a possibility that excipients that are commonly found in adult formulations are not safe when added to pediatric formulations even in very small concentrations [8]. Excipients such as colorants, preservatives, ethanol, sweeteners, and propylene glycol can be harmful to children, especially for infants and neonates. Due to this, risk-based assessment should be conducted to excipients added in pediatric formulations [9]. The development of pediatric medicines should only require a small number of excipients as well as a minimum amount of each excipient added in the formulation to avoid the risk of toxicity.

As drug-drug interaction in pediatricians can be life threatening, planning for the assessment of potential interaction must be part of every pediatric drug development program is very important. However, studies that involve pediatric drug-drug interactions are rarely conducted for ethical and practical reasons and unfortunately, exposure to multiple medications in children, specifically the ones who are hospitalized, increases the risk and experience of drug-drug interactions [10]. For this reason, this study emphasizes the need to identify DDI potential and management of DDIs in the pediatric patients through a review on the overall safety and acceptability of pediatric drugs in the market.

Methodology

This article review utilized a well-organized literature assessment to identify evidenced-based, recent, and published journals. The articles primarily focus on the importance, development, evaluation, considerations, and regulation of pediatric drug formulations found in ResearchGate, Elsevier, Google Scholar, PubMed, Sage Journals, and other databases. The article search started on July 5, 2022. After the collection of substantial information, pertinent data were systematically organized and comprehensively evaluated based on their importance, validity, and applicability in accordance with the topic of the review; thus, filling the gaps in the research. A repeated review of the manuscript is done to produce appropriate changes prior to accessing any journal database for publication.

Results and Discussions

- Differences between Pediatric Drug Formulations from Adult Drugs Formulations

The readiness and accessibility of drugs with pediatric indications have been falling behind those medications for adults for years. Moreover, formulations that cater to children's ability and willingness to take are commonly insufficient, especially for the younger ones. Hence, to alleviate the problem, the pediatric investigation plan (PIP) published by the European Medicines Agency (EMA) in 2013 obliges pharmaceutical companies to develop more than one formulation in treatment for any children's age and status of the disease. According to the European Medicines Agency QWPPC, it requires the industry to justify all facets of pediatric medicine design. Such aspects include the route of administration selection, dosage form type, concentration of the product, frequency of the dosing, composition of the excipient, etc [11]. According to Batchelor and Marriott, the added requirements and needs make the development of pediatric formulations more complex than for adults. Furthermore, the pharmacodynamic and pharmacokinetic drug profile varies generally which is determined by the child's developmental stage. Hence, it is a necessity that these formulations have dose flexibility to complement the dosing demands suitable for all pediatric age classifications [12].

Doctors often reduce the dose of an adult medication, utilize a lesser dose concentration, or choose a compounded formulation where production errors are possible if a licensed drug is unavailable for the pediatric population. Specifically, the variation between children and adults essential to dosing and formulation of a drug product are water content of the body, metabolism and gastric emptying rate, hepatic clearance, weight, height, and sensitivity to ingredients. For instance, the differences in water

content of the body in children may cause pharmacokinetic changes, which influence the distribution of the drug. The group may also have different expressions of transporters and enzymes that affect the drug's absorption, distribution, metabolism, and excretion (ADME) which compromise it and the safety of the excipients. In formulation, changing a dosage form for easier swallowing or lowering the dose for children can result in unstable drug products and insufficient bioequivalence in comparison with the formulation for adults, which further contributes to the unpredictable drug behavior [13]. The children's anatomy and physiology differences can affect the drug performance, which is unlike what was observed in adults. Consequently, the said differences should be taken into consideration in pediatric formulation design to avoid compromising drug pharmacokinetic profiles. This is predominantly essential to neonates and infants who are farthest from adult development [14].

- Pediatric Drugs Formulation Considerations

In contrast with adults, the pediatric population has different needs and more demands. Hence, pediatric medicines necessitate special considerations in developing drug formulations. The development is a difficult task due to the specific requirements of pediatric age groups with regard to dosage, convenience, and acceptability and the wide-ranging aspects of both clinical and pharmaceutical. The considerations of these aforementioned assure patient compliance [14] and products that are of quality, safe, and effective [12]. Specified below are the considerations for developing safe and acceptable pediatric drug formulations.

  - Physiological Considerations

1. Pediatric Patients Variability

According to Ivanovska et al., the development of age-applicable pediatric drug formulations is difficult due to the heterogeneity among the different age groups of the pediatric population. They differ greatly in terms of taste inclinations, adverse drug reactions, and medical conditions. These variations can affect the dosages and dosage forms needed. Due to their physiologic body differences, the active components and excipients also affect them differently [15]. For instance, neonates have distinct physiological variations from older children and adults that impact medication; ADME. These variations may also be influenced by disease and its severity, special treatments, and developmental alterations of specific organ drug transporters, as stated by Mooij et al. In addition, according to Mulla, neonatal physiology variations can potentially impact pharmacodynamics, which results in variations in the anticipated potency, effectiveness, or toxicity of medications. Children have varying cognitive capacities as they grow, which will impact how well they comply with their regimen [16].

2. Saliva-Flow Rate

Saliva must be present for oral and oral transmucosal drugs in order for them to be absorbed. The release of drug, dissolution, and absorption are facilitated by the aqueous condition provided by saliva. Bradley further explains that both the flow rate and content of saliva are inclined to alter during a person's lifetime. Up until around 5 to 6 years of age, the saliva-flow rate is likely to rise; after that, it drops while the average electrolyte content increases, according to Gutman and Ben-Aryeh. Furthermore, according to Sonesson etal., children secrete saliva at a rate (0.22-0.82 mL/min) that is much lower than adults (0.33-1.42 mL/min) in the buccal mucosa. The level of salivary hydration and the difficulty swallowing medicine/s are directly correlated [15].

3. Gastrointestinal Tract (GIT) pH Values and Drug Absorption

According to Yoder et al., after the intake of any pharmacological substance, they undergo numerous processes prior to elimination from the body system. The organ system that transports, digests, absorbs, and eliminates them is called the gastrointestinal (GI) tract, which involves the oral cavity, esophagus, stomach, and intestines. To attain safe and efficacious therapeutic doses of drugs, it is critical in medicine to understand the anatomical and physiological distinctions of GI system components between children and adults. The information from physiological variations will also help regulatory evaluations and better guide the development of pediatric drugs, as stated by Yu et al [17]. The GIT's pH differs in accordance with the tissue's location and the age of the patient. Generally, the pH rises as the rate of salivation increases. As an example, the mean pH of the oral mucosa of adults is (6.78 ± 0.04), while in children is (6.64 ± 0.44) [15].

a. Oral cavity

A short and wide tongue is common among newborns and descends into the oropharynx by the time a child is 4 years old, as stated by Singh. In addition, the larynx which is located in a higher area descends during the development, and the pharynx connects with both the food passage and the airway, increasing the risk of aspiration, as described by Matsuo and Palmer. According to EMA, the younger age groups in the pediatric population cannot easily take solid oral dose forms as a result of this developmental transition and motor skill deficiencies. Furthermore, the oral cavity size would also hinder the size and volume of the dose [17].

b. Esophagus

The primary physical esophageal variations seen between children and adults are their length and diameter wherein the younger the child, the shorter the size. These variations may affect the overall transit time. For instance, since children have a shorter esophagus, food contents will be emptied into the stomach faster. Significantly, according to Margolis and Picoraro, the outspread of peristaltic movements and the lower esophageal sphincter is underdeveloped at birth, which can result in common symptoms of gastroesophageal reflux disease (GERD) throughout the neonatal period. This can fluctuate the transit time and change the total concentration of medicine essentially getting into the stomach as regurgitation happens or several contents may be ejected out through the mouth [17].

c. Stomach

The variations between adults' and children's stomach physiology can have an influence on the absorption of drugs. These differences which are pH of gastric acid, fluid volume, and gastric emptying can affect, especially the weakly acidic pharmacologic substances absorbed in the stomach. During infancy, the gastric acid output is reduced compared to adulthood, which results in an elevated gastric pH, as described by Lu and Rosenbaum. Moreover, according to them, when children's gastric pH is increased, and medications that would normally be completely in their undissociated state and are easily absorbed by the gastric acids, may instead have lower bioavailability. On the other hand, higher pH levels may protect medications that are sensitive to acid and promote the bioavailability of weak bases. Stomach emptying in neonates is slower and less consistent than it is in adults. They may experience slow or deferred absorption due to the increased gastric emptying rate, shortened bowel transit time, and decreased intestinal absorption surface area, as stated by Lu and Rosenbaum. Also, the stomach's capacity rises with age. According to Bar-Shalom et al., this is crucial for low-solubility BCS Classes II and IV medications since a greater volume of gastric acid will result in higher dissolution quantities [17].

d. Intestine

According to Fernandez et al., children's physiology in the intestine differs from adults' in several ways resulting in differences in abilities for drug absorption among the two. The length of a newborn's small intestine is about 300–350 cm and has quantitatively much fewer circular folds (plicae circulares), as stated by Lander and Newman. By delaying the movement of partially digested food, these folds enhance the absorption's surface area and lengthen intestinal transit time, enabling efficient digestion and adequate absorption. According to Ginsberg et al., intestinal permeability is high during birth, with rates three or four times greater than in adults because of an inadequate mucosal barrier caused by the underdeveloped intestinal mucosa, as described by Michielan and D'Incà. Batchelor and Marriott claimed that gut flora affects metabolism and GI movements, and alterations in bacterial colonization can have an impact on bioavailability. The pediatric population would develop a mature gut flora environment by the age of 4, according to Hollister et al and Ringel-Kulka et al. The transport mechanisms are undeveloped at birth, which causes a range of absorption levels. According to Mulberg et al., at about 4 months of age, both active and passive transport systems are fully developed [17].

- Pharmacokinetic Considerations

The growth and development of a human cause changes in the pharmacokinetic processes of ADME. As a matter of fact, the modifications in ADME may have effects that are detrimental on drug delivery, resulting in toxicity or subtherapeutic consequences. To elaborate, the pediatric population is a dynamic group in terms of physiology, particularly in the neonatal through infant phases of development. The difference in pharmacokinetic characteristics between children and adults can have a significant impact on the resulting concentration of the pharmacological substance (e.g. drug or excipient) [17].

1. Absorption

   Due to variations in GI tract growth, absorption, which is the initial physiological mechanism that determines the level of bioavailability, can differ from one individual to another. Fernandez et al. described that surface area, intestine permeability, stomach pH and emptying, GI movement, underdeveloped intestinal mucosa, transport mechanisms, and bile secretion are factors that influence the degree of absorption. According to Lange et al., the absorption and amount of weakly basic, weak organic acids and/or pharmaceutical substances that are easily destroyed in an acidic environment might notably fluctuate due to the shift in stomach pH throughout growth and development [17].

   The neonates, according to Strolin Benedetti and Baltes, exhibit greater Intestinal transit (IT) time due to decreased GI motility and peristaltic wave frequency, whereas infants exhibit decreased IT time due to enhanced GI motility. The short time of IT may prevent the pharmaceutical agent from having enough time to be fully absorbed through transporters actively and passively, which leads to lower concentrations [17], especially for poorly soluble medications or sustained release drugs, as illustrated by Grand et al. [14]. Furthermore, according to Arzani et al., the production of bile salts is inhibited in neonates and infants, leading to a diminished capacity to solubilize and absorb lipophilic medications and compounds [17]. In addition, according to Kearns et al., because of the thinner stratum corneum that allows more absorption of medication/s and greater surface area to volume ratio of infants, they are more susceptible to drug toxicity through skin absorption [18].

2. Distribution

   Drug distribution in children is often influenced by development disparities in the organ maturation rates, perfusion of blood, the proportion of extravascular water, fat percentage of the body, differential penetration rates into tissues, and illness conditions, as explained by Hoppu et al. [19]. Furthermore, it is also affected by body composition. According to Puig, due to the greater comparative amounts of fat in infants, they have a considerably greater volume of distribution for lipophilic medicines than older children do. On the other hand, as extracellular water reduces with development, from 70% of total body weight in newborns to 61.2% in one year old, hydrophilic medicines likewise have higher volumes of distribution in preschoolers. In order to obtain equivalent plasma and tissue concentrations in infants compared to adults, greater doses per kilogram body weight of water-soluble medications must be administered, according to Brown and Campoli-Richards [14]. In addition, according to Sanders et al., because the blood brain barrier (BBB) is still developing in newborns, there is a considerably higher risk of toxicity due to chemicals (drugs and/or excipients) penetrating the central nervous system in high concentrations (CNS). Also, given that plasma protein binding ability is lower in newborns than in adults, there may be more pharmacological substances accessible for activity, as indicated by the larger proportion of unbound drugs detected in neonates, as described by Ku and Smith [17].

3. Metabolism

   The primary organ in charge of metabolism is the liver, wherein drugs are converted into relatively more safe and water-soluble molecules, facilitating elimination via urine and bile. Depending on how much enteric and liver metabolic processes are concerned, alterations in metabolizing capability during development can have an impact on both bioavailability and elimination, according to Leeder. Neonates have suppressed enzyme production and function due to underdeveloped metabolizing enzymes, raising the risk of drug buildup (toxicity), as claimed by Zanger and Schwab. According to de Wildt et al., children ages 6 to 12 months have around half the quantity of CYP metabolizing enzymes that adults do. The volume of blood flowing through the liver also has an impact on hepatic clearance; in a newborn, hepatic blood flow is decreased, but by infancy, it is equivalent to that of adults. Nevertheless, due to a larger liver proportion to bodyweight ratio through the infancy/preschool period, the hepatic clearance of drugs is greatly improved, as described by Lammert et al. [17].

4. Elimination

   Renal elimination is lowest in neonates and steadily rises as the renal system develops. The blood flow in the kidney rises with age as well, reaching adult-like levels by the time a child is two years old, as stated by Gandhi et al. In newborns, the GFR is at its minimum level, but rises quickly during the two weeks after birth and reaches maturation after one tyear, according to Muhari-Stark and Burckart. Moreover, tubular reabsorption rises, reaching its peak between 1-3 years of age. According to Strolin Benedetti et al., active tubular secretion is also underdeveloped in neonates but reaches adult levels by 7 to 12 months. The degree and mode of excretion are influenced by a number of variables, including plasma protein binding, solubility in water, and molecular weight, as added by Lu et al. [17]. For instance, minimal protein binding in neonates will accelerate the clearance of drugs through these renal mechanisms because there are larger amounts of unbound medication that exist [16].

- Pharmacodynamic Considerations

Pharmacodynamics includes the physiological and biological reaction to the medication and is not usually directly connected to pharmacokinetics, whereas pharmacokinetics involves the ADME of the drug that may be assessed by blood/plasma samples. For coherent dosing, it is essential to understand the connection between children's pharmacokinetics and pharmacodynamics. Validated endpoint measures for children are required for pharmacodynamic analysis [14]. Both efficacy and toxicity of the drugs should be considered. For example, the children's pharmacological development and receptors can influence the wanted effect of the drug, through the main action mechanism, and any far-off results- desired, neutral, or toxic .

- Formulation Development Considerations

The formulation considerations for pediatric drugs is by creating safe and effective dosage formulations for children, which can be complicated based on their unique needs, and by selecting the most appropriate formulation in relation to the patient's age, which is one of the primary issues in creating the pediatric dosage forms. Its dosing regimen, for example; dose accuracy, flexibility, frequency, etc.; the route of administration, dosage forms, and the compatibility and stability of the excipients should be properly considered. The last two factors have a significant impact because of the non-compliance with oral and buccal dosage forms that is well-known in the pediatric population due to swallowability and palatability [20].

On the other hand, due to their potency, doctors do not advise tablets and capsules for pediatric patients under the age of four; the available tablets for older pediatric children might not have the appropriate strength. Although breaking or splitting tablets is a widespread practice, it does not ensure proper dosage. Additionally typical is the administration of oral dosage form suspensions or solutions to young patients. Lozenges, candies, chewing gum, and lollipops are some of the additional buccal dosage forms. Using it impromptu to make liquid formulations is an option if a commercial liquid is unavailable. Moreover, pediatric formulation compounding, specifically for newborns, is difficult to administer. When treating the newborn patients, the shortage or lack of appropriate medicine is one of the main problems. The preparation of oral medicine for children in various hospitals varies substantially since formulas and stability information on preparation are not standardized.

Consequently, bulk powders and tablets can be used as a stand-in for commercialized pediatric dosage forms when they are not available. To produce a formulation that is both safe and efficient for pediatric patients, the formulation's components must be understood. As propylene glycol content has a high powder content, lorazepam bulk powder can be used to prepare oral solutions for young patients but not commercially produced injections. For newborns, high propylene glycol dosages are dangerous. Moreover, it is important to comprehend the ingredients, additives, and excipients before using tablets as a drug source to create oral solutions or suspensions. It has the capacity to thicken it. To attain the desired rheology, the concentration must be diluted.

- Regulation

Careful drug medication development and clinical investigations involving pediatric patients are essential for the creation of the proper pediatric dose forms and for the protection of public health. Doctors have two options when a treatment isn't allowed for use in children: either treat the patients with drugs that are based on adult research with little pediatric experience, or refrain from treating the children with potentially helpful drugs that aren't approved for use in pediatric medicine. The Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA), which are headquartered in the United States of America, regulate pediatric drug development legislation. The FDA is currently mandating early integration in the creation of new pharmaceuticals. While the Best Pharmaceuticals for Children Act (BPCA) offers financial incentives for

the businesses to undertake pediatric studies voluntarily, the Pediatric Research Equity Act (PREA) mandates that companies test the safety and effectiveness of novel medications and biologics in pediatric patients [21].

Furthermore, investigations on adults are routinely conducted in order to guarantee the bioavailability of the pediatric formulation. Clinical studies are conducted on children once the effectiveness and safety of the treatment have been evaluated in adults. Because pediatric patients come in a wide range of ages and sensitivity levels, pediatric clinical trials should be cautious and properly designed. Pediatric kids may suffer from a variety of medical issues, unexpected side effects, and unforeseen bad effects if the procedure is not carried out appropriately [22].

Tools for measuring therapeutic outcomes for patients of different ages, the development of patients' cognitive, physical, and emotional systems, research procedures, and locations should all adhere to ethical and legal requirements while developing a clinical trial protocol. Since there may not always be many kids with the same medical conditions, it may be challenging for parents to understand and accept that kids are participating in research. Oral dose forms with innovative release properties, such those created by pharmaceutical companies, can make things more difficult. These dosage forms could contain excipients that are unsafe for use in pediatric patients, so pediatric patients might not be able to use them. Because it makes the regulatory process more difficult, testing on children is not appropriate [23]. Because of this, it is not acceptable to test on children as it complicates the regulatory process. Pharmaceutical companies may request a partial PREA waiver from the FDA if dosage forms in specific circumstances are too big for kids to swallow. The firms must have made every attempt to produce a pediatric formulation necessary for the given age group in order to qualify for a partial PREA waiver. Therefore, to ensure compliance with PREA requirements, it is crucial to evaluate and begin thinking of a pediatric-friendly dosage form as soon as possible.

Further discussions

This will provide the findings of various relevant studies upon which concerns the pediatric formulations available in the market, relating to their overall safety and acceptability for its intended audience.

- Potentially-Harmful Medications for Pediatrics

In a study by Meyers et al. [24], a KIDs list has been created with the intent of being able to list down potentially harmful drugs on pediatric patients, thereby providing a standardization in the provision of care for its safe usage. This is to make sure that the adverse drug reactions (ADR) that may be experienced from the administration of these medications be minimized, or eventually, eradicated. Accordingly, it is directed towards medical professionals who care for patients under 18 years old in acute and long-term institutional, ambulatory, and community settings. The said list of drugs, also found in the WHO Model of Essential Medicines for Children, is provided in the consecutive tables:

Drug	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Atazanavir[51]	Kernicterus	Caution in neonates unless pharmacogenetic testing is used	Weak	Very low
Benzocaine[52–57]	Methemoglobinemia	Avoid in infants for teething or pharyngitis	Strong	High
Camphor[58–60]	Seizures	Caution in children	Weak	Low
Carbinoxamine[61]	Death	Avoid in <1 year	Strong	Low
Ceftriaxone[62,63]	Kernicterus	Caution in neonates	Weak	Very low
Chloramphenicol[64]	Gray baby syndrome	Avoid in neonates unless serum concentration monitoring is used	Strong	High
Chlorhexidine[65]	Chemical burn	Caution in very low birth weight neonates	Strong	Low
Codeine[66–69]	Respiratory depression, death	Avoid in children unless pharmacogenetic testing is used	Strong	High
Darunavir[70]	Seizures, death	Avoid in <3 years or <10 kg	Strong	Very low
Daptomycin[71]	Neuromuscular and skeletal adverse events	Caution in <1 year	Weak	Very low
Dicloxacillin[72]	Kernicterus	Caution in neonates	Weak	Very low
Dicyclomine[73]	Apnea	Avoid in <6 months	Strong	Low
Difluprednate[74,75]	Increased intraocular pressure	Caution in children	Weak	Low
Diphenoxylate and atropine[76]	Respiratory depression, death	Avoid in <6 years	Strong	Moderate
Dopamine antagonists Chlorpromazine[77] Fluphenazine[77] Haloperidol[77,78] Metoclopramide[77,81–88] Perphenazine[77] Pimozide[77,78,87] Prochlorperazine[77,79,83,88–90] Promethazine[91–93] Trifluoperazine[77] Trimethobenzamide[94]	Acute dystonia (dyskinesia); increased risk of respiratory depression, extravasation, and death with intravenous use	Avoid in infants Caution in children	Strong: Chlorpromazine Fluphenazine Haloperidol Perphenazine Pimozide Prochlorperazine Promethazine Trifluoperazine Weak: Metoclopramide Trimethobenzamide	Moderate
Gentamicin ophthalmic ointment[95–97]	Severe ocular reactions	Avoid in neonates	Strong	High

Table 1. KIDs Table from Atazanavir to Gentamicin ophthalmic ointment on their risks/rationale, recommendation, strength of recommendation (weak to strong), and quality of evidence (very low to high), as provided by Meyers et al. [24]

In this table, data suggests that the strength of recommendation varied from strong (10 drugs) and weak (6 drugs), with quality of evidences shown to be ranging from very low (5 drugs), low (5 drugs), moderate (2 drugs), and high (2 drugs) levels.

Drug	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Hexachlorophene[98]	Neurotoxicity	Avoid in neonates	Strong	High
Indinavir[99]	Nephrolithiasis Hyperbilirubinemia	Avoid in children Avoid in neonates	Strong Strong	High Low
Ivermectin (oral)[100,101]	Encephalopathy	Avoid in <1 year	Weak	Low
Lamotrigine[102]	Serious skin rashes	Caution in children; titration needed	Strong	High
Lidocaine 2% viscous[103,104]	Seizures, arrhythmia, death (due to CNS depression, seizures, or dysrhythmias)	Avoid in infants for teething	Strong	High
Linaclotide[105]	Death from dehydration	Avoid in <6 years	Weak	Very low
Lindane[106,107]	Seizure, spasm	Avoid in <10 years or <50 kg	Moderate	Low
Loperamide[108]	Ileus, lethargy	Avoid in infants for acute infectious diarrhea	Strong	High
Macrolides[109–112] Azithromycin Erythromycin (oral and intravenous)	Hypertrophic pyloric stenosis	Avoid in neonates, unless treating *Bordetella pertussis* (azithromycin), or *Chlamydia trachomatis* pneumonia (azithromycin and erythromycin) Consider risk/benefit ratio when using for ureaplasma (azithromycin)	Strong	High
Malathion[113]	Increased absorption (organophosphate poisoning)	Avoid in <1 year	Weak	Very low
Meperidine[114,115]	Respiratory depression	Avoid in neonates Caution in children	Strong	High
Midazolam[116]	Severe intraventricular hemorrhage, periventricular leukomalacia, or death	Avoid in very low birth weight neonates	Strong	High
Mineral oil, oral[117]	Lipid pneumonitis	Avoid in <1 year	Strong	Low
Naloxone[118,119]	Seizure	Avoid in neonates for postpartum resuscitation	Strong	High
Nitrofurantoin[120,121]	Hemolytic anemia	Avoid in neonates	Weak	Very low
Olanzapine[122]	Metabolic syndrome (weight gain, hyperlipidemia, hyperglycemia)	Caution long-term use (>24 weeks) in children	Strong	High
Opium tincture[123]	Respiratory depression	Avoid in neonates Caution in children	Strong	High

Table 2. KIDs Table from Hexachlorophene to Opium tincture on their risks/rationale, recommendation, strength of recommendation (weak to strong), and quality of evidence (very low to high), as provided by Meyers et al. [24]

In table 2, it can be seen that there are only four drugs with a weak strength of recommendation (Ivermectin, Linaclotide, Malathion, and Nitrofurantoin), and one drug with a moderate level (Lindane). For the quality of evidence, the data varied from very low (3 drugs), low (4 drugs), to high (10 drugs).

Drug	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Paregoric[123]	Gasping syndrome, seizures, CNS depression, hypoglycemia	Avoid in children	Strong	High
Plecanatide[124]	Death from dehydration	Avoid in <6 years	Weak	Very low
Propofol[125–130]	Propofol-related infusion syndrome; higher rate in children than adults because higher relative doses of propofol are needed, especially in status epilepticus	Avoid doses >4 mg/kg/hr for greater than 48 hours	Strong	Moderate
Salicylates[42,131–134] Aspirin Bismuth subsalicylate Choline magnesium trisalicylate Magnesium salicylate Methenamine, sodium phosphate monobasic, phenyl salicylate, methylene blue, and hyoscyamine Methyl salicylate (topical) Salicylic acid Salsalate	Reye's syndrome	Caution in children with suspicion of viral illness (influenza and varicella)	Weak	Very low
Sodium phosphate solution, rectal (enema)[135,136]	Electrolyte abnormalities, acute kidney injury, arrhythmia, death	Avoid in infants	Strong	High
Sodium polystyrene sulfonate[137,138]	Colonic perforation	Avoid in very low birth weight neonates	Weak	Low
Sulfonamides Silver sulfadiazine[139] Sulfadiazine[139] Sulfamethoxazole[72,140]	Kernicterus	Avoid in neonates except as adjunctive therapy with pyrimethamine as a treatment of congenital toxoplasmosis (sulfadiazine)	Weak	Very low
Tetracyclines[141–147] Demeclocycline Tetracycline	Tooth discoloration (demeclocycline and tetracycline)	Caution in <8 years	Strong	High
	Enamel hypoplasia (tetracycline)	Caution in <8 years	Strong	High
	Retardation of skeletal development and bone growth in premature neonates (tetracycline)	Caution in neonates	Strong	Moderate

Table 3. KIDs Table from Paregoric to Tetracyclines on their risks/rationale, recommendation, strength of recommendation (weak to strong), and quality of evidence (very low to high), as provided by Meyers et al. [24]

In this table, there are only four drugs with a weak strength of recommendation (Piecanatide, Salicylates, Sodium polystyrene sulfonate, and Sulfonamides). Meanwhile, the quality of evidences mostly varied from very low to moderate levels, except for Tetracyclines on tooth discoloration and enamel hypoplasia, Sodium phosphate solution, and Paregoric with high levels of evidence quality.

Drug	Risk/Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Topical corticosteroids (medium, high and very high potency)[148,149]	Adrenal suppression; higher rate of systemic absorption in children than adults	Avoid in <1 year for diaper dermatitis	Strong	Low
Tramadol[66,150]	Respiratory depression	Caution in children unless pharmacogenomic testing is used	Weak	Low
Tricyclic antidepressants[151–153] Desipramine Imipramine	Sudden cardiac death	Avoid in children (desipramine) Caution in children (imipramine)	Strong	High (desipramine) Moderate (imipramine)
Valproic acid and derivatives[154–156]	Pancreatitis, fatal hepatotoxicity	Avoid in infants Caution in <6 years	Strong	High
Verapamil[157–159]	Asystole	Avoid in <1 year	Weak	Low

Table 4. KIDs Table from Topical Corticosteroids to Verapamil on their risks/rationale, recommendation, strength of recommendation (weak to strong), and quality of evidence (very low to high), as provided by Meyers et al. [24]

In this table, it can be seen that the strength of recommendations are relatively strong, except for Tramadol and Verapamil, with a relatively low quality of evidence, except for the tricyclic antidepressants with a high (desipramine) and moderate (imipramine) value.

Excipient	Rationale	Recommendation	Strength of Recommendation	Quality of Evidence
Benzyl alcohol, sodium benzoate, benzoic acid[33,34,160–163]	Gasping syndrome	Avoid exposure of >99 mg/kg/day in neonates (with the exception of sodium phenylacetate/ sodium benzoate used for the treatment of urea cycle disorders)	Strong	High
Ethanol/ethyl alcohol[34,164] (this excludes ethanol lock)	CNS depression, hypoglycemia	Caution in <6 years; maximum of 5% vol/vol ethanol with clinician supervision	Strong	Moderate
Isopropyl alcohol[165,166]	Chemical burn	Caution in very low birth weight neonates	Strong	Low
Methylparaben, propylparaben[167]	Kernicterus	Caution in <2 months	Strong	Very low
Phenylalanine[168]	Cognitive and behavioral problems	Avoid in children with an unknown phenylketonuria test	Strong	High
Polysorbate 80[169–171]	E-Ferol syndrome	Avoid in <1 year (any amount)	Strong	High
Propylene glycol[33,34,172,173]	Lactic acidosis, CNS depression, hypoglycemia, hemolysis, seizure	Avoid doses >3 g/day in neonates; caution doses >34 mg/kg/day in neonates	Strong	Moderate

Table 5. KIDs Table from Benzyl alcohol, sodium benzoate, and benzoic acid to Propylene glycol on their risks/rationale, recommendation, strength of recommendation (weak to strong), and quality of evidence (very low to high), as provided by Meyers et al. [24]

Finally, this table provides a consistently strong strength of recommendation amongst the excipients provided, with a varying quality of evidence ranging from very low (1 drug), low (1 drug), moderate (2 drugs), to high (3 drugs).

In line with the data aforementioned, the study of Liu et al. [25] provides a comparison on the safety of antipsychotic and antidepressant drugs between adult and pediatric populations. According to the table, there are drugs that recorded more ADRs in pediatrics compared to adults, as follows:

Drugs	Age range of pediatric patients	Patient number in pediatric clinical trials	Patient number in adult clinical trials	ADRs (pediatric patients > adults)
Aripiprazole	6–18 y	732 (pooled)	1843 (pooled)	Abdominal pain, diarrhea, salivary hypersecretion, fatigue, pyrexia, decreased appetite, increased appetite, sedation
Duloxetine	7–17 y	476	4797 (pooled)	Abdominal pain, vomiting, weight increased, decreased appetite, headache, oropharyngeal pain
Paliperidone	12–17 y	150 (pooled)	850 (pooled)	Sedation
Lurasidone 40 mg	13–17 y	110	487	Respiratory tract infection
Lurasidone 80 mg	13–17 y	104	538	Respiratory tract infection
Escitalopram	12–17 y	234	715	Abdominal pain, vomiting, inflicted injury, respiratory tract infection, headache, menstrual cramps
Risperidone (bipolar I disorder)	10–17 y	111	448	Blurred vision, abdominal pain, diarrhea, dyspepsia, nausea, vomiting, fatigue, increased appetite, dizziness, sedation, pharyngolaryngeal pain
Risperidone (schizophrenia)	13–17 y	106	564	Salivary hypersecretion, extrapyramidal disorder, sedation,
Asenapine	10–17 y	302	620	Blurred vision, abdominal pain, oral hypoesthesia, irritability, dehydration, dyspnea, fatigue, increased appetite, myalgia, headache, dysmenorrhea, sedation, anger, pharyngolaryngeal pain, rhinitis, rash, tachycardia

Table 6. Drugs that have been found to have more ADRs in pediatrics than adults, by Liu et al. [25]

Weight gain, weariness, orthostatic hypotension, and tachycardia are other ADRs that are listed but not included in the chart. These side effects have a negative impact on the chance that pediatric patients will tolerate and take their drugs as prescribed [25].

The long-term effects of this discrepancy in ADRs in pediatric patients are currently unknown due to the uneven therapy received by adult and pediatric patients in the modern world. But according to the authors, this must be disclosed to pediatric healthcare professionals and evaluated in upcoming pharmacovigilance programs and drug development studies of new antipsychotic and depression medications in pediatric patients [25].

Pharmacodynamic Differences in Children	
	Effect
Absorption	Oral absorption is generally similar in older infants and children compared to adults.[4]
Distribution (Body Fat)	Proportion of body fat is the highest in the first year of life, followed by a steady decrease during early/middle childhood, until an increase occurs pre-pubertally. A lower proportion of body fat leads to a smaller volume of distribution, while a higher proportion of body fat leads to a larger volume of distribution. For example, most psychotropic medications (antidepressants and antipsychotics) are lipophilic. The lower proportion of body fat in middle childhood results in a smaller volume of distribution, and thus *higher* plasma drug concentrations
Distribution (Body Water)	Proportion of body water(total and extracellular) is high in infancy and decreases with age. For drugs primarily distributed in body water (e.g. - lithium), the higher proportion of body water in childhood results in a larger volume of distribution, and thus *lower* plasma drug concentrations.
Metabolism	• **Phase I**: CYP450 enzyme activity develops in the fetal period and infancy, and increases in childhood to above adult levels, and then declines after puberty to adult levels. The greater CYP450 activity during childhood results in lower plasma drug concentrations (other factors being equal and adjusting the dose for weight) • **Phase II**: Glucuronide formation reaches adult levels by age 3-4 years; thereafter the efficiency of phase II reactions does not vary with age
Elimination	GFR is much lower in newborns, but reaches adult values by age 6-12 months. Children have lower absolute clearance than adults because of their smaller body size, but evidence is mixed on whether children have higher weight-adjusted clearance compared to adults.[5]

- Pharmacodynamics in Pediatrics (as compared in adults)

Table 7. Differences in Pharmacodynamics as found in children, provided by Fernandez et al. [26]

Pharmacodynamically, this table provides sufficient data on its differences in pediatrics, since when compared to adults, children often have faster metabolisms and elimination rates. For the majority of drugs, this means that children typically need higher weight-adjusted dosages in order to obtain blood levels that are comparable to those of adults. The volume of distribution is also increased for the majority of psychiatric medications. Due to this, a strategy wherein the dosage is started low and administered gradually slow is crucial since pharmacokinetics in children is difficult to anticipate [26].

The many aspects that must be taken into account when creating age-appropriate drugs have been divided into three groups: those that have to do with patient safety, patient efficacy, and patient access. A flexible technology platform is desired to enable the creation of formulations with various active pharmaceutical ingredients (APIs), dose strengths, and/or release profiles because it is unlikely that a single formulation development approach will be suitable for all patients given the number of parameters that must be satisfied. The criteria mentioned are elaborated in the table below:

Table 8. Product requirements on the aspects to be considered for age-appropriate drugs as provided by Lopez et al. [27]

Benefit/risk	Criterion for drug product	Product requirements
Efficacy/acceptability	Dosage	Dose flexibility Acceptability of size/volume
	Preparation/administration	Easy and convenient handling Easily administered (correct use)
	Compliance	Minimal impact on lifestyle Acceptable appearance and taste Minimal administration frequency
Patient safety	Bioavailability	Adequate bioavailability
	Excipients	Minimal number of excipients Tolerability
	Stability	Stable during shell life Stable in-use
	Medication error	Minimal risk of dosing error
Patient access	Manufacturability	Robust manufacturing process Commercial viability
	Affordability	Acceptable cost to patient and payers Easily transported and stored Low environmental impact

The same study provided that age-appropriate oral formulations must be able to satisfy both the needs of the patient individually, as well as the quality criteria for traditional pharmaceutical medications (i.e. a higher degree of flexibility in dose and ease of swallowing, among others). Apart from that, medicine delivery focused highly upon the patient may also be

considerably advantageous for adults and geriatric patients who have diminished ability to ingest standard solid formulations. Therefore, to enable high-quality products while ensuring that patients have access to better treatments, a balanced strategy between innovation and cost-effectiveness is needed.

- Utilization of Pharmacokinetic Model for Pediatric Drug Approval (Pre and Post)

In connection with the aforementioned data, there is enough provided evidences on drug-medication interactions (DDIs) in children endangering and threatening their quality of life, hence every pediatric drug development program needs to include an assessment of the interaction potential. The article by Salerno et al. (2019) has suggested strategies for evaluating pharmacokinetic/pharmacodynamic DDIs throughout pediatric drug development and clinical use. DDI studies are, however, rarely carried out in the pediatric population for ethical and practical reasons, despite the paucity of information available regarding pediatric DDIs [28].

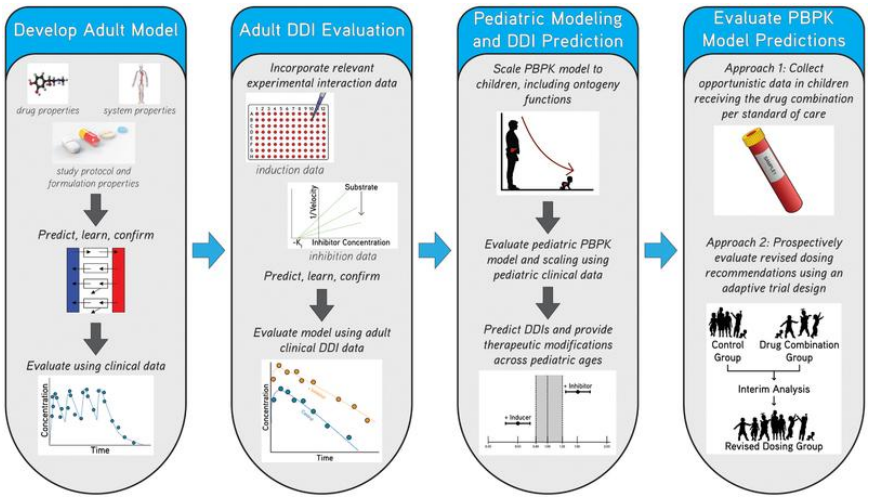

Figure 1. Physiologically-based Pharmacokinetic (PBPK) model for DDI prediction, as provided by Salerno et al. [28]

As per the model in figure 1, the application of physiologically-based pharmacokinetic (PBPK) modeling and simulation to predict drug-drug interaction (DDI) potential in pediatric patients is the main recommendations of the authors, wherein PBPK models based on adults are to be scaled in accordance with the data of pediatric patients and evaluated accordingly. From there, pediatric patients' data can be used to replicate DDIs to provide therapeutic suggestions, dosing recommendations, and monitoring of the efficacy and safety of dosages and drug combinations to make changes in response to the results [28].

As a result, the provided model can be used to assess whether a pediatric drug should be approved. It applies dose adjustments in advance, and the Population Pharmacokinetic (PopK) model inserts itself here so that concomitant medications can be assessed as predictors of individual variability in pharmacokinetic parameters. Following drug approval, studies utilizing real-world data can be carried out to assess the dosage appropriateness, PK changes, safety, and efficacy in kids receiving the target drug combination in accordance with standard of care, as provided in figure 2, as follows:

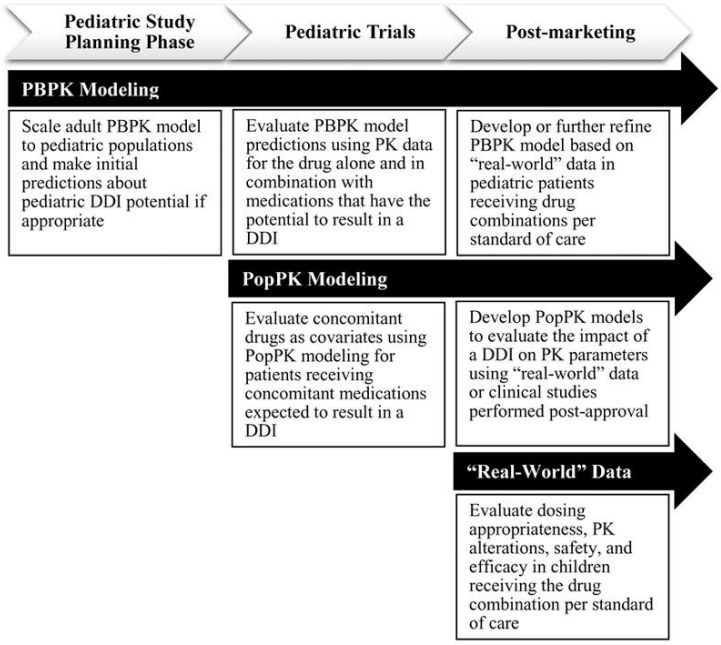

Figure 2. Evaluation Model on Pediatric-Pharmacokinetic DDIs from pediatric drug development towards post-pediatric drug approval, as provided by Salerno et al. [28]

Conclusion

For a very long time, developing pediatric medications has been difficult, especially for newborns and young infants. Because of all the factors that must be taken into account before developing a drug, it becomes complicated. Finding the right dosage form for the patient's age is one of the biggest issues. There is a lack of information regarding the acceptability of various dosage forms, volume, dosage form size, and particular flavor.

As the discussions suggest, considerations on the patient safety, patient efficacy, and patient access should be taken into account when formulating age-specific drugs especially for the pediatric population. Also, it was found out that pediatrics have faster metabolism and elimination which suggest that children require higher weight-adjusted dosages.

Moreover, a Pharmacokinetic Model to predict drug-drug interaction in pediatric drugs is utilized to support any pediatric drug whether it should be approved or not. This eases the process of formulating medication for the pediatric population for it assesses how the drug interacts with other drugs and at the same time, how it reacts to the body of the children.

Medication for young patients differs markedly from that for adult patients. As a result, creating such medications can be difficult and should be done with care. Studies are continuously conducted to produce better pediatric medications that are really suitable for every patient considering their age, weight, preference, and such. However, commercially-available pediatric formulations can be expected to be safe and effective as it already has undergone tests. This is ensured by models such as the PBPK model for DDI prediction and a further evaluation model on the Pediatric-Pharmacokinetic DDIs from its development and beyond.

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