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Parenteral preparations for administration in the pediatric population: the challenges of excipients selection

Danina Krajišnik*

University of Belgrade – Faculty of Pharmacy, Department of Pharmaceutical Technology and Cosmetology, Vojvode Stepe 450, 11221 Belgrade, Serbia

*Corresponding author: Danina Krajišnik, e-mail: danina.krajisnik@pharmacy.bg.ac.rs

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Abstract

The need for the development of age-appropriate preparations for patients under 18 years of age is important to ensure appropriate therapy for all children via different routes of administration. Parenteral administration of medicinal products in the pediatric population is common in hospitalized patients, in emergency situations or when the (per)oral route of administration is not possible. The development of a drug formulation for parenteral administration in children requires the consideration of the route of administration (related to physiological differences between children and adults), the site of action and the duration of the pharmacological action of the active substance, the volume of the preparation and the general health condition of the patient. A major challenge in the formulation of these preparations is the selection of excipients that should ensure adequate product quality and patient tolerability.

The paper presents an overview of considerations related to the formulation of parenteral preparations for the pediatric population. The regulatory requirements regarding the use of excipients with confirmed effects and the labeling of preparations containing them are listed. Also, modern approaches (databases and tools) that can be useful for the selection of appropriate excipients were considered.

Key words: parenteral preparations, age-appropriate formulations, excipient selection, excipient safety, labeling

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Introduction

Parenteral administration of medicinal products in the pediatric population is common in critically ill young children (e.g. premature infants or neonates) or in situations where children are unconscious or unable to swallow medicines due to disease or damage to the mouth or gastrointestinal tract. In addition, the drug can be administered parenterally if (per)oral administration is not possible due to instability or enzymatic degradation in the gastrointestinal tract or if a rapid onset of action is required (1).

The most common routes of parenteral administration of drugs in the pediatric population are intravenous, subcutaneous or intramuscular (2). Several factors must be considered when administering drugs parenterally: the route and site of administration, the volume of the drug, and the general condition of the patient. In addition, the properties of the parenteral preparation such as pH, buffering, osmolarity, viscosity, and, if relevant, the needle thickness and needle length should be described and justified (3). As it is common in clinical practice for medicinal products for use in children to be prepared by reconstitution or dilution of medicinal products intended for use in adults, all factors that may affect the accuracy, safety and efficacy of such therapymust be considered. Therefore, considerations regarding the specifics of the formulation of parenteral preparations in the pediatric population are of great importance.

Formulation of parenteral preparations for administration in children

The need for age-appropriate preparations for patients under 18 years of age is necessary to ensure adequate therapyfor all children via different routes of administration, dosage forms, and medicine strengths (4, 5). However, the development of pediatric-specific dosage forms is particularly challenging due to a variety of factors that differentiate this population from the adult population (6). To date, several guidelines have been published in both the European Union (EU) and the US that require consideration of the formulation in the pediatric study plan (PSP) or pediatric investigation plan (PIP) (3, 7–10). For injectable formulations, appropriate drug concentrations should be developed to allow accurate and safe administration of the dose (11). It is well known that pediatric pharmacology has always been a special field of research, not only for the study and development of active ingredients, but also for excipients (12). The most important factors relevant for the formulation of pediatric dosage form are presented in Figure 1.

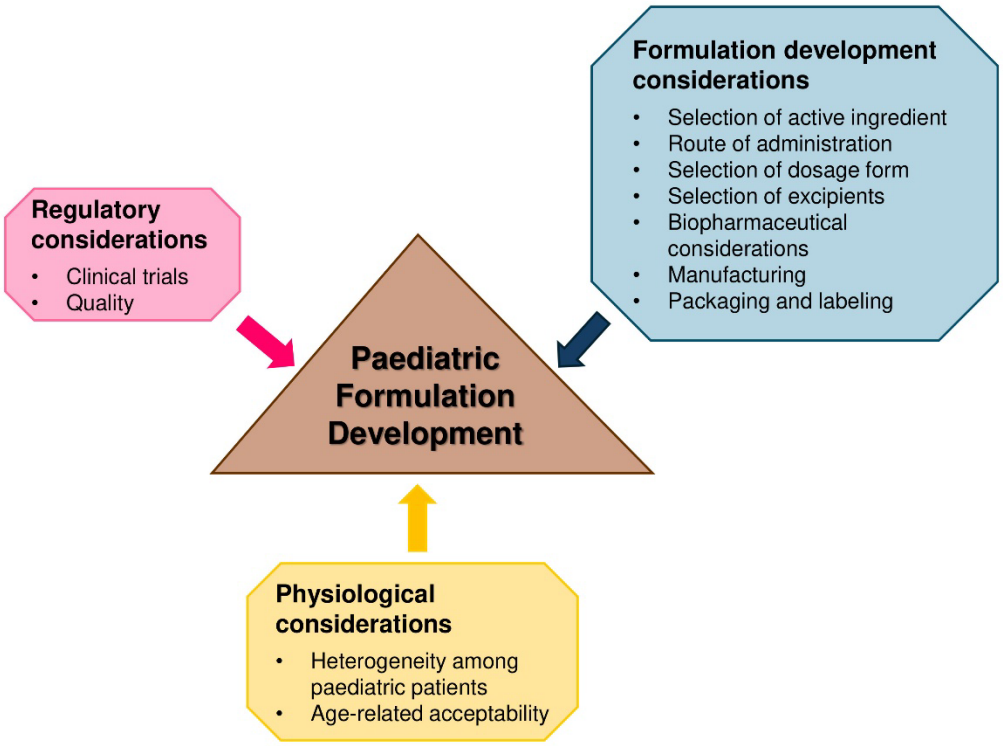

Figure 1. The most important factors relevant for pediatric formulation development
Slika 1. Najznačajniji faktori za fazvoj formulacije pedijatrijskog leka

The general approach in the formulation of parenterals is to maintain the simplicity of a formulation, i.e. to use only the necessary excipients. According to the general monograph on *Parenteral preparations* of Ph. Eur. (13), the excipients should not adversely affect the intended medicinal action or, at the concentrations used, cause toxicity or undue local irritation. Also, parenteral preparations intended for chronic use or total parenteral nutrition should have appropriate limits for specific components or elements, taking long-term toxicity into account.

This also applies to the formulation of pediatric medicines for parenteral application. The excipients in the formulation are selected to ensure performance, stability, microbial control and other considerations necessary to support product quality (14). Although excipients should be pharmacologically inactive, it is known that certain excipients are not suitable for use in parenteral preparations for children as the physiology of neonates and infants differs considerably from that of adults (11). In addition, the daily intake of certain excipients may exceed the safe daily intake limit per kilogram of the child's body weight, and cumulative intake must be taken into account for long-term (chronic) use (15).

Excipients in parenteral preparations for administration in children

The selection of excipients for the formulation of medicinal products intended for use in the pediatric population must be performed with serious caution. Low-birth-weight

neonates, infants, asthmatics and diabetics are examples of several subgroups of the pediatric population that are likely to be hospitalized and receive therapy via the parenteral route of administration. Therefore, critically ill neonates and children are at risk of exposure to much higher levels of harmful (known or potential) excipients than critically ill adults (16, 17). In these patient groups in particular, examples of adverse reactions related to the use of certain excipients were recorded. Many of these reactions were related to the quantity of excipients used in a dosage form in terms of acute toxicity and repeated cumulative exposure in terms of chronic toxicity (18). Therefore, excipients used should have defined safety profiles, including considerations of potential toxicity, effects on organ development, duration of exposure and potential accumulation, and general tolerability in pediatric patients (3, 11, 14, 19–21).

Examples of functional categories of excipients used with caution in parenteral preparations for the pediatric population are preservatives, co-solvents, emulsifiers or substances that increase solubility (Table I).

Table I Examples of excipients that are used with caution in parenteral preparations for pediatric population and their recognized adverse action or effect (15, 21)

Tabela I Primeri ekscipijenasa koji se oprezno koriste u sastavu parenteralnih preparata za primenu u pedijatrijskoj populaciji i njihovo potvrđeno neželjeno delovanje ili efekat (15, 21)

Excipient	**Functional category**	**Adverse action or effect**
polyethylene glycol	solvent	metabolic acidosis
propylene glycol	solvent	seizures, neurotoxicity, hyperosmolarity, hypotension, arrhythmia, hemolysis, lactic acidosis
ethanol	solvent	neurotoxicity
polysorbate 20 and 80	surfactant	liver and kidney failure
cyclodextrins	complexing agents/solubility enhancer	renal toxicity
macrogolglycerol-ricinoleate (*cremophor el*)	surfactant	severe anaphylactic reactions
benzyl alcohol	preservative	neurotoxicity, metabolic acidosis, respiratory depression
thiomersal	preservative	allergic hypersensitivity reactions
chlorocresol metacresol	preservatives	may cause allergic reactions.
sulfites, bisulfites	antioxidants	asthma attack, rashes
fructose	tonicity adjustment	hereditary fructose intolerance
sorbitol	tonicity adjustment	hereditary fructose intolerance

Although water for injection is the preferred solvent in the formulation of parenteral preparations, the poor solubility of many active pharmaceutical ingredients requires the use of co-solvents or other excipients that increase solubility. Propylene glycol, polyethylene glycol or ethanol are examples of co-solvents that are used more frequently. Propylene glycol is used in parenteral preparations as a co-solvent for poorly soluble substances (e.g. phenobarbital, phenytoin or diazepam) or in multivitamin concentrates. Pediatric patients under 4 years of age have a limited metabolic pathway (reduced alcohol dehydrogenase activity), resulting in the accumulation of propylene glycol, with a prolonged half-life in children (16.9 hours) compared to adults (5 hours). Parenteral administration of propylene glycol in neonates and infants can lead to various adverse effects (both biochemical and clinical), such as hypotension, arrhythmia, hemolysis, serum hyperosmolality, and central nervous system depression (19–22). Ethanol is one of the excipients used as a co-solvent which raises concern of health regulatory bodies worldwide, as it causes neurotoxicity and cardiovascular problems in the pediatric population. Therefore, ethanol should not be included in the formulation of medicines for children without a clear demonstration of benefit (14). There are strict limits in pharmaceutical preparations containing ethanol administered via oral, inhalation and parenteral route (23).

The use of polysorbate 80 as an emulsifier (at a dose > 72 mg/kg/day) was associated with several neonatal deaths in the USA in the 1980s following intravenous administration of vitamin E preparations (24, 25). Nowadays, polysorbate 20 and 80 are one of the most frequently used excipients in biotherapeutic formulations and their safety data in adults are well documented. Although polysorbates are generally considered non-toxic, non-irritant, and non-carcinogenic, i.e. well tolerated, there are reports of hypersensitivity and hepatoxicity due to highly dosed polysorbates used as excipients (26, 27). Macrogolglycerol-ricinoleate is another representative of a non-ionic surfactant used as a solubilizer in parenteral preparations. However, it can cause severe allergic reactions after parenteral administration (23). Egg-lecithin used as an emulsifier in an injectable propofol emulsion can cause allergic reactions in children with a history of egg allergy (28, 29). Although this type of adverse reaction is very rare, it is recommended that patients with a history of egg anaphylaxis receive an alternative anesthetic instead of propofol or start with a small trial dose of propofol. If this is well tolerated, the full anesthetic dose can then be reached gradually (30).

Cyclodextrins (CD) are complexing agents that are used to increase the solubility of active ingredients in aqueous parenteral preparations. However, β-cyclodextrin (β-CD) has been associated with nephrotoxicity when administered parenterally, especially at high doses (31). The low water-solubility of β-CD is a cause for its precipitation in aqueous solutions, which is particularly unacceptable in solutions for parenteral administration since they must be free of visible particles. Furthermore, this microcrystalline precipitation of β-CD can occur in the kidney in addition to the irreversible cellular damage that β-CD causes in renal cells, which eventually results in its nephrotoxicity (32). As this is a major limitation to the use of β-CD in parenteral

preparations, safer derivatives such as sulfobutyl-ether-β-cyclodextrin (SBE-β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD), have been developed, which have lower toxicity and better renal tolerance (33, 34). HP-β-CD is a derivative produced by the substitution of several hydroxyls at both extremities of the β-CD molecule, which reduces its crystallinity, and improves both its water-solubility and toxicological profile. SBE-β-CD is a polyanionic β-CD derivative, characterized by the substitution of various hydroxyls on the β-CD molecule for sulfobutylether groups. As HP-β-CD, this derivative has an improved water-solubility and safety, compared to its native β-CD, which enables its pharmaceutical application, especially in parenteral formulations. Both β-CD derivatives have found applications in registered injectable dosage forms such as Sporanox® (which contains HP-β-CD for solubilization of itraconazole) and Vfend® (which contains SBE-β-CD for solubilization of voriconazole) (32). The safety aspects of cyclodextrins should have been considered during the development and safety assessment of the specific drug products and should therefore be clearly stated in the Summary of Product Characteristics (SmPC). Because there is insufficient information on the effects of cyclodextrins in children < 2 years old, a case-by-case judgement should be made regarding the risk/benefit for the patient (23, 35).

Benzyl alcohol, which is used as a preservative in small-volume parenteral preparations, can cause pain at the application site and hypersensitivity reactions. In addition, the metabolic pathways for its elimination in the liver are still immature in neonates, which can lead to the accumulation of benzoic acid with potentially fatal consequences. Therefore, experts currently recommend that the use of benzyl alcohol in parenteral preparations in children under 3 years of age should only be permitted after careful considerations (15). Benzoic acid, sodium benzoate, and potassium benzoate as preservatives in parenteral preparations may increase the risk of jaundice in neonates (11). Thiomersal is a preservative frequently used in vaccines. However, several allergic hypersensitivity reactions (e.g. erythema, vesicles) have been reported. Health authorities have recommended that this preservative should be removed from vaccines due to the risk of toxicity (19). Metacresol, used as a preservative in insulin preparations, caused cutaneous erythema and skin breakdown at injection sites in a 12-year-old pediatric patient (36).

Sulfites are antioxidants that are widely used in various pharmaceutical preparations. Although they are considered as safe excipients by regulatory authorities, they can pose a risk and cause various clinical side effects in children, ranging from slight flushing and hypotension to severe hypersensitivity reactions and bronchospasm (19, 21, 23).

Sorbitol, which is commonly used as a tonicity adjusting agent in parenteral preparations, is metabolized to fructose, and is therefore contraindicated in pediatric patients with hereditary fructose intolerance (21).

The European Commission (EC) released a guideline on “Excipients in the Labelling and Package Leaflet of Medicinal Products for Human Use” in 2018 (37), while the last revision (Revision 4) of this document was published in 2024 (23). It contains a

list of excipients with a known action or effect, which must appear on the labeling of medicines in the European Union, and the information which should appear in the package leaflet. The threshold value, included in the Annex, is a value equal to or above which it is necessary to provide the information stated. However, it is not a safety limit. A threshold of “zero” means that it is necessary to state the information in all cases where the excipient is present in the medicinal product. Except where otherwise stated, thresholds are expressed as the quantity of excipients at the Maximum Daily Dose (MDD) of the medicinal product as indicated in the SmPC.

Useful information to aid the development of specific drug products related to the selection of appropriate excipients can be found in the Food and Drug Administration’s (FDA) Inactive Ingredient Database (IID) which contains information on inactive ingredients in FDA-approved drug products (38). This database defines the Maximum Daily Exposure (MDE) as the total amount of the excipient that would be taken or used in a day based on the maximum daily dose (MDD) of the drug products in which it is used. The MDE is calculated as the dosage unit level of the excipient multiplied by the maximum number of recommended dosage units per day (excipient (mg) x number of units). The MDE may also be referred to as the Maximum Daily Intake (MDI) for oral drug products. The guidance document (39) provides recommendations how to use the IID in the development of drug products and how it can be useful in evaluation of excipient safety. According to this document, the maximum potency of excipients in parenteral dosage forms is also shown as a percentage of the total formula weight, in which percentage is the percent weight per volume (% w/v). Excipient potencies of parenteral products that are marketed as powders or lyophilized powders for reconstitution are generally shown as the percentage of the excipient in the product after reconstitution.

For a certain number of parenteral excipients, MDE can be found in the IDD. However, this database is constantly updated with the approval of new drug products. Furthermore, MDE can be higher for certain drug products which are not registered by the FDA, but are registered by another regulatory agency (e.g. European Medical Agency (EMA)). Therefore, it is important to consult all relevant databases when analysing the safety of potential excipient (39).

Table II lists examples of excipients with known actions or effects that must be labeled on the outer packaging of the medicinal product and in the package leaflet, as well as restrictions on their use in parenteral preparations for pediatric patients (23).

Table II Examples of excipients with a known action or effect which must appear on the labeling of medicines in the European Union (EU) (adapted according to ref. 23)

Tabela II Primeri ekscipijenasa sa poznatim delovanjem ili aktivnošću koji se moraju navesti pri obeležavanju lekova u Evropskoj uniji (prilagođeno prema ref. 23)

Name	**Threshhold**	**Information for the Package Leaflet**	**Comments**
benzoic acid (E 210) and benzoates* e.g.: sodium benzoate (E 211) potassium benzoate (E 212)	Zero	<Benzoic acid / Benzoate salt> may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).	Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).
benzyl alcohol*	Zero	Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children. Do not give to your newborn baby (up to 4 weeks old), unless recommended by your doctor. Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.	Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("gasping syndrome"). The minimum amount of benzyl alcohol at which toxicity may occur is not known. Warning in section 4.4 in the SmPC should be given if used in neonates. Increased risk due to accumulation in young children.
cyclodextrins# e.g.: alfadex betadex (E 459) γ-cyclodextrin sulfobutyl-ether-β-cyclodextrin (SBE-β-CD) hydroxypropyl betadex randomly methylated β-cyclodextrin (RM-β-CD)	20 mg/kg/day	This medicine contains x mg cyclodextrin(s) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight> <volume>>. Do not use in children less than 2 years old unless recommended by your doctor.	Cyclodextrins (CDs) are excipients which can influence the properties (such as toxicity or skin penetration) of the active substance and other medicines. Safety aspects of CDs have been considered during the development and safety assessment of the drug product, and are clearly stated in the SmPC. There is insufficient information on the effects of CDs in children < 2 years old. Therefore, a case-by-case judgement should be made regarding the risk/benefit for the patient. Based on animal studies and human experience, harmful effects of CDs are not to be expected at doses below 20 mg/kg/day.

cyclodextrins[§] e.g.: alfadex betadex (E 459) γ-cyclodextrin sulfobutyl-ether-β-cyclodextrin (SBE-β-CD) hydroxypropyl betadex randomly methylated β-cyclodextrin (RM-β-CD)	200 mg/kg/day and use for > 2 weeks	If you have a kidney disease, talk to your doctor before you receive this medicine.	In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of cyclodextrins. In patients with moderate to severe renal dysfunction accumulation of cyclodextrins may occur.
fructose[◊]	Zero	If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose in this medicine, which may cause serious side effects. You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhea.	Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary. Babies and young children (below 2 years of age) may not yet be diagnosed with HFI. Medicines (containing fructose) given intravenously may be life-threatening and must be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.
organic mercury compounds[§] e.g.: Thiomersal Phenylmercuric nitrate/acetate/borate	Zero	This medicinal product contains (thiomersal) as a preservative and it is possible that <you/your child> may experience an allergic reaction. Tell your doctor if <you/your child> have/has any known allergies. Tell your doctor if you/your child have/has experienced any health problems after previous administration of a vaccine.	See EMEA Public Statement, 8 July 1999, Ref. EMEA/20962/99 Additional statement to be mentioned for vaccines.
polysorbates[§] e.g.: PS 20 (E 432) PS 80 (E 433) PS 40 (E 434) PS 60 (E 435) PS 65 (E 436) PS 85	Zero	This medicine contains x mg of polysorbate <type> in each <dosage unit><unit volume> <which is equivalent to x mg/<weight> <volume>>. Polysorbates may cause allergic reactions. Tell your doctor if <you have><your child has> any known allergies.	

	3 mg/kg/day (total amount of all PS in the medicinal product)	Polysorbates can have an effect on your heart and blood circulation (e.g., irregular or abnormal heartbeat, or low blood pressure).	Risk minimization by lowering the rate of injection/infusion is recommended for consideration in the SmPC of parenteral products. Due to a potential for QT prolongation and torsades de pointes in humans, for risk minimization, a SmPC warning on the risk of concomitant use of medications that prolong the QT/QTc interval or for patients with congenital syndrome should be considered.
	35 mg/kg/day (total amount of all PS in the medicinal product)	Polysorbates may have an effect on the liver. If you have a liver disease, ask your doctor or pharmacist for advice.	Case reports in adults indicate an onset of signs of hepatotoxicity (elevated liver enzymes) at a cumulative daily dose of 35-40 mg/kg. In neonates, doses > 80 mg/kg/day of polysorbate caused severe (fatal) hepatotoxicity.
propylene glycol (E 1520) and esters of propylene glycol*	1 mg/kg/day	If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol.	Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.
	50 mg/kg/day	If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they use other medicines that contain propylene glycol or alcohol.	Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.
	500 mg/kg/day	Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects. Do not use this medicine in children less than 5 years old. Use this medicine only if recommended by a doctor. Your doctor may carry out extra checks while you are taking this medicine.	Various adverse events, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnea; liver dysfunction; hemolytic reaction (intravascular hemolysis) and hemoglobinuria; or multisystem organ dysfunction, have been reported with high doses or prolonged use of propylene glycol. Therefore doses higher than 500 mg/kg/day may be administered in children > 5 years old but will have to be considered case by case. Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following hemodialysis. Medical monitoring is required.

sorbitol◊ (E 420)	Zero	Sorbitol is a source of fructose. If you (or your child) have HFI, a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects. You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhea.	Patients with HFI must not be given this medicine unless strictly necessary. Babies and young children (below 2 years of age) may not yet be diagnosed with HFI. Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

*route of administration: oral, parenteral; # route of administration: all; § route of administration: parenteral; ◊ route of administration: intravenous (IV)

Within the last revision, new information related to polysorbate was included, which is very important, since the use of this excipient is growing in parenteral preparations for both adult and pediatric populations.

Despite the aforementioned risks and limitations related to the use of excipients in parenteral preparations for administration in children, recent literature has reported examples of adverse effects. Saito et al. (41) investigated the quantitative exposure of potentially harmful excipients via injection and their association with adverse events in children under 2 years of age. The results of the study revealed that for benzyl alcohol, glycerol, polyethylene glycol, and polysorbate higher doses of these excipients were related to adverse event occurrence and that more precise information on potentially harmful excipients for pediatrics including neonates is necessary. Polyethylene glycol (PEG) has been recently used as an excipient in a broad spectrum of application. One of the important aspects of its use is in the PEG-modified (PEGylated) drugs which have been registered for application in pediatric population (42). Although allergic reactions to PEG are not commonly described, safety issues become significant due to the presence of PEG in the messenger ribonucleotide acid (mRNA) COVID-19 vaccine (43, 44).

Selection of appropriate excipients: current possibilities and future perspectives

It is clear from the above that the consideration of the excipient's safety in the formulation of parenteral preparations for children is of crucial importance. Therefore, collaboration between pharmaceutical experts in this field is essential during formulation development to consider the number of excipients, their content and the appropriate route of administration (45). As a result of the collaboration between the European Pediatric Formulation Initiative, (EuPFI) and the United States Pediatric Formulation Initiative (US-PFI), the Safety and Toxicity of Excipients for Pediatrics (STEP) database was

created (46). This database stands out with respect to other public sources (e.g. Vitic, Symyx, AcTOR etc.) regarding the complete and/or comparative information on safe use and acceptability of excipients in pediatrics (19, 47). The STEP database is a repository for all the scientific communities with information that facilitate access to data (e.g. use and acceptability of excipients in children) and enables rapid evaluation of the risks associated with the use of a specific excipient (19, 47). Since its launch in 2014 as a pilot version with 10 excipients, the STEP database has rapidly grown into an essential resource, now serving more than 3,000 registered users from 44 countries. By providing comprehensive and reliable safety data, the STEP has significantly impacted pediatric medicine development by reducing costs and accelerating the creation of life-saving treatments for children. As a result, several pharmaceutical companies have integrated the database into their research, leading to improved drug safety and simplified regulatory approval processes. This database is recognized as a trusted resource by global regulatory authorities, such as the EMA, Health Canada, and the Chinese Centre for Drug Evaluation. Due to its growing popularity and global impact, the STEP has secured funding from the USA National Institute of Health to support further expansion. The next version, STEP 2.0, will leverage advanced AI and machine learning models to automate processes, ensuring ongoing updates and refinements. This integration of advanced technology is expected to maintain database integrity, enhance data accuracy, and expand the number of excipients available for review (48).

The Pediatric Excipients Risk Assessment (PERA) framework is another systematic approach for selecting excipients and assessing the risk exposure to excipients. This framework provides a structured, systematic decision-making approach using adaptable tools and processes that can help improve transparency and communications in the selection and justification of excipients used in a pediatric formulation (49).

Agrawal et al. (5), presented a case study on the application of the PERA tool for the selection of the excipient for parenteral administration to neonates. In this case, the active compound under clinical development was a crystalline powder with poor solubility in water at physiological pH, necessitating the use of an excipient that would improve solubility and enable the formulation of a solution for intravenous administration. Two different β-CD derivatives were investigated: SBE-β-CD and HP-β-CD, which showed to have better renal safety compared to β-CD when administered intravenously. The limitations related to use of cyclodextrins in pediatric populations are being established by regulatory authorities (23, 34). SBE-βCD was selected over HP-β-CD due to the physicochemical properties of the active compound to be solubilized, the chemical stability and the inclusion constant stability of cyclodextrins, and the possibility of terminal sterilization (32). The PERA tool was used to assess patient attributes (age and body weight, disease type and severity, dosing regimen, co-medications and preconditions) and product and dosing attributes (route of administration, dosage form, dosing approach, environment of use, packaging and delivery device). The outcome of the PERA tool was to conduct an additional study to mitigate the safety/potential alert related to the Acceptable Daily Intake (ADI) value considering the target concentration

of the active compound to be dissolved and the potentially high CD concentration required for complete solubilization in a limited volume of fluid for neonatal administration. The conclusion from this case study was that additional safety studies are required before this excipient can be used for neonatal administration or that the formulation approach may need to be modified. Finally, the PERA framework and tool can potentially have an important role in promoting best practices for the selection and risk-benefit assessment of excipients for pediatric medicinal products.

In general, the selection of appropriate excipients for formulation of pediatric drug product is not simple and straightforward and it requires a thorough search of the literature. In addition to previously described sources such as the Inactive Ingredient Database (IID) (37), PharmaCircle database (50), SmPCs monograph, product prescribing information, and product patents can be of great help. Since up-to-date treatment in pediatrics often involves a personalized approach, i.e. off-label and unlicensed pediatric formulations (21), as well as nano-carrier (42, 51) and protein-based therapeutics (52), the use of such bases and tools will become increasingly important in the selection of pharmaceutical excipients for the pediatric population.

Off-label drug use is defined as any use of a drug under conditions different from the dose stated in the Summary of Product Characteristics (SmPC) approved by the EMA. Therefore, off-label use can represent deviations from indications, administration routes, age or weight of a patient, dose or frequency of administration or the pharmaceutical dosage form used (53). The literature reports that at least one third of children in hospital and up to 90% of newborns in neonatal intensive care units receive off-label prescriptions, and therefore it can be considered as common in pediatrics (54). Unlicensed drug use involves the use of a drug that has never been granted marketing authorization, such as the use of compounded preparations (e.g. in a hospital pharmacy department) or use of investigational therapy (e.g. drugs under study, but not yet approved for clinical practice by regulatory authorities) (53). Although off-label and unlicensed prescriptions in the pediatric population could be beneficial because there are currently limited authorized drugs for this population, this is a big concern regarding patients' safety (55, 56). According to the British National Formulary for Children (BNFC), special care is required when managing childhood conditions with unlicensed medicines or with licensed medicines used for unlicensed indications. Such use should be supported by appropriate evidence and experience (57). In many cases of unlicensed or off-label use, cautionary and advisory labels regarding excipients in non-proprietary preparations are provided. For example, *Co-trimoxazole solution for infusion* may contain alcohol, propylene glycol or sulfites; *Dexamethasone solution for injection* may contain disodium edetate or propylene glycol; *Diclofenac sodium solution for injection* may contain benzyl alcohol or propylene glycol. The BNFC also stated that responsibility for the appropriate use of medicines lies solely with the individual health professional, further emphasizing the importance of suitable excipient selection (57).

Nanomedicine holds significant potential for addressing the unique challenges of diagnosing and treating pediatric diseases. The formulation approaches used in marketed

nanomedicines for pediatric applications include liposomes, nanocrystals, polymeric nanoparticles, pegylated nanoparticles, lipid nanoemulsions, and polymeric lipid hybrid nanoparticles (42, 58). The intrinsic physiological and compliance differences between adults and pediatric patients add complexity to pediatric formulation design. Limited dosage form options, excipient selection, safety concerns, and challenges in clinical trial design and execution are factors that must be carefully considered. Therefore, knowledge of excipient safety profile is a mandatory requirement by regulatory agencies to avoid any potentially toxic or unsuitable excipients in nanomedicines for children. Additionally, the preparation methods of nanocarriers are also important since safe and easy-to-scale-up preparation methods can limit the use of organic solvents and produce safe carriers (59).

In a review paper by Saito et al. (60), the current state, challenges, ongoing efforts, and future perspectives of pharmaceutical excipients for pediatric patients in several countries and regions (Africa, Australia, Canada, China, Europe, Japan, and the USA) are presented. The authors conclude that the excipients used in pharmaceutical products are reviewed by regulatory authorities in each country or region. The preparation of harmonized guidelines and a unified excipient database would be helpful for regulatory authorities and healthcare professionals. Furthermore, clearer safety limits are especially important for neonates, young children, and patients who receive multiple and long-term treatments, where potential and cumulative adverse effects are of great importance. Collecting evidence-based data for the preparation of the evidence-based excipient regulation is recognized as imperative.

Pediatric clinical trials of medicinal products and devices used in children should be designed to meet the rigorous standards of the competent authorities. Therefore, there are regulatory, scientific, and ethical reasons to address the knowledge gap regarding the efficacy and safety of medicines in the pediatric population. High-quality clinical trials involving children of all ages are expected to generate data that will ultimately close these knowledge gaps and support decision making (61). The development and validation of pediatric formulations for specific populations (e.g., neonatal patients) are particularly relevant and important. For neonates, it is important to consider the exposure to excipients as well as to active ingredients, i.e. to assess the circulating concentration-time profile rather than rely on quantitative information about the excipient content of the product. Clinical trials can be used to gather data about excipients to compare exposures associated with new products to those in registered products which are known to be safe. However, careful attention should be given to the relevance of age, dose, route of administration, and disease (62).

Conclusion

The formulation of pediatric medicines for parenteral administration is a complex task, as their use is associated with high risks. The selection of excipients with appropriate safety and tolerability is a major challenge in the development of parenteral preparations considering the safety profile of the excipient for the target age group, the route of administration, the single and daily dose of the excipient, duration of treatment,

acceptability for the intended pediatric population and the regulatory status. Excipients such as solvents, preservatives, surfactants and solubility enhancers are recognized as excipients with known effects, and therefore, their use in the composition of pharmaceutical preparations and labeling must be in accordance with regulatory guidelines. Excipient safety databases and risk assessment tools developed over the last decade can greatly assist in the evaluation and selection of appropriate excipients for the formulation of parenteral preparations for use in the pediatric population.

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Declaration of Competing Interest

The author declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Danina Krajišnik: Conceptualization, Writing – original draft, review & editing.

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Parenteralni preparati za primenu u pedijatrijskoj populaciji: izazovi izbora ekscipijenasa

Danina Krajišnik*

Katedra za farmaceutsku tehnologiju i kozmetologiju, Univerzitet u Beogradu – Farmaceutski fakultet, Vojvode Stepe 450, 11221 Beograd, Srbija

*Autor za korespondenciju: Danina Krajišnik, e-mail: danina.krajisnik@pharmacy.bg.ac.rs

Kratak sadržaj

Potreba za razvojem lekova koji su prilagođeni uzrastu pacijenata mlađih od 18 godina je važna da bi se obezbedila adekvatna terapija kada se lekovi primenjuju različitim putevima primene. Primena lekova parenteralnim putem u pedijatrijskoj populaciji česta je kod hospitalizovanih pacijenata, u urgentnim stanjima ili u situacijama kada nije moguć (per)oralni put primene. Pri razvoju formulacije leka za parenteralnu primenu kod dece neophodno je uzeti u obzir put primene leka (povezan sa fiziološkim razlikama između dece i odraslih), mesto delovanja i dužinu trajanja farmakološkog efekta aktivne supstance, zapreminu preparata i opšte zdravstveno stanje pacijenta. Veliki izazov u formulaciji ovih preparata predstavlja izbor ekscipijenasa koji treba da obezbede odgovarajući kvalitet proizvoda i podnošljivost od strane pacijenta.

U radu je dat prikaz razmatranja vezanih za formulaciju parenteralnih preparata za primenu u pedijatrijskoj populaciji. Navedeni su regulatorni zahtevi koji se odnose na primenu ekcipijenasa sa potvrđenim dejstvom i obeležavanje preparata koji ih sadrže. Takođe, razmotreni su savremeni pristupi (baze podataka i alati) koji mogu biti od koristi pri izboru odgovarajućih ekscipijenasa.

Ključne reči: parenteralni preparati, formulacije prilagođene pedijatrijskom uzrastu, izbor ekscipijenasa, bezbednost ekscipijenasa, obeležavanje