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# A Research on the Additives and Regulatory Requirements for Pediatric Formulation

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***Abstract***

*These days, pediatric considerations are incorporated early on in the creation of new medications. The guidelines and policies of European drug regulatory bodies served as the foundation for our investigation. The review comprehensively outlines excipients commonly found in pediatric medicine formulations. It identifies potentially harmful compounds flagged by scientific literature, stressing the necessity of rigorous safety checks, often involving toxicity studies. Excipients included in pediatric databases, like the STEP database, prioritize safety and toxicity considerations. This compilation ensures medications administered to children meet stringent safety standards. By emphasizing these factors, we aim to enhance the safety and efficacy of pediatric medications, advancing the field of pediatric medicine while safeguarding the well-being of young patients. Addressing the challenges surrounding diethylene glycol (DEG) and ethylene glycol (EG) as excipients encompasses understanding their complex physicochemical properties, navigating toxicity concerns, and adhering to stringent regulatory requirements. Emphasis is placed on implementing safety precautions to mitigate associated hazards. Moreover, compliance with legal mandates governing their use in medications is paramount. This multifaceted approach ensures the safe integration of DEG and EG into formulations, bolstering confidence in their efficacy and safety profiles. By tackling these challenges head-on and fostering compliance with regulatory standards, we strive to enhance the quality and safety of medications utilizing these excipients.*

**Keywords:** Pediatric, active pharmaceutical ingredients, excipients, medications, dosage, FDA, EMA, Clinical studies.

## INTRODUCTION

The word “PAEDIATRIC” is derived from Greek word, meaning “Healer of Children”. This area of medicine focuses on the health and sickness needs of children from conception to adolescence. It focuses on child prevention, promotion, treatment, and rehabilitation [1–7].

- In the field of medicine, pediatric formulation plays a crucial role in providing appropriate medications for children.
- Due to variations in physiology and developmental factors, the treatment of pediatric patients requires careful consideration and customization.
- Pediatric formulations differ from those used for adults, as they often need to be adjusted in terms of dosage, formulation composition, and taste to ensure therapeutic efficacy and patient compliance.

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- Additionally, the use of additives in pediatric formulations plays a significant role in enhancing stability, palatability, and safety of medications for children.
- The importance of pediatric formulation and additives in catering to the specific needs of pediatric patients, emphasizing their crucial role in providing effective treatment options for children.

Creating excipients for pediatric use is a challenging procedure that has to take a number of factors into account in order for them to be suitable variables [8–10]. It is also necessary to take into account the changes in different organs, body composition, protein bonding, active transport systems, and metabolic pathways that are linked to children's rapid growth and development.

Not only is this a challenging process, but it is also an essential one in the creation of pediatric formulations as several acceptable excipients used in adult patient formulations are inappropriate for use in pediatric formulations.

It is thus of particular relevance to carry out an assessment of safety of excipients prior to their use in pediatrics. Animal toxicity studies should also be conducted for non-clinical safety investigations in juveniles, since they offer a comprehensive evaluation of clinical risk.

Pharmaceutical firms can thus cooperate to create a reference list of excipients widely regarded as safe for use in pediatric formulations, and filter the demands for safety evaluations by choosing those that will contribute to a possible therapeutic benefit. The process of making clinical decisions will be facilitated in this way [11, 12].

The primary goal of this theoretical study is to critically examine the use of excipients in pediatrics, with a focus on safety issues. By doing so, information will be gathered that will help make judgments about the expert creation of formulations. There are several reviews and regulatory guidance on detail formulation options and their suitability for children age ranges between 4–8 and 9–11 years respectively (Figure 1).

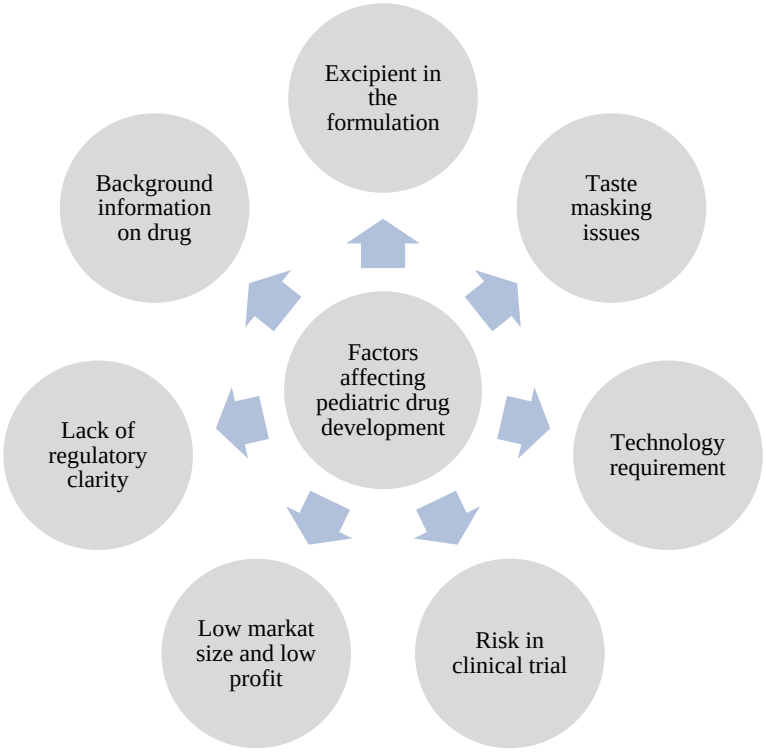


**Figure 1.** Factors affecting of pediatric formulation.

 

**Types of Pediatric Formulations**

There are three types of pediatric formulations:

1. Solid dosage form:
   i. Tablet (chewable),
   ii. Capsule, and
   iii. Oro dispersible formulation.
2. Liquid dosage form:
   i. Solutions,
   ii. Suspension, and
   iii. Elixirs and Syrup.
3. Gaseous dosage form:
   i. Inhalers, and
   ii. Nebulizers.

## FACTORS AFFECTING PAEDIATRIC DRUG DEVELOPMENT

### Additives

Pharmaceutical additives are substances that are not actually part of the product but are added on purpose to enhance certain aspects of it. They can also be described as inactive substances that are used to carry the active ingredient in medicines; additives can also be used to facilitate the manufacturing process [13].

The regulatory control regarding the use of additives is still not clear as compared to active pharmaceutical ingredient. There is a strong need of regulation and legislation for additives so as to avoid the unnecessary adverse effects and interaction with the drugs. So, the additives should go through the various evaluations like toxicity study, preclinical study, compatibility studies etc. [14, 15]. Not all additives are inert substances; some have been shown to be potential toxicants.

## IDEAL CHARACTERISTICS OF ADDITVES

1. It should be inert in nature.
2. It should be physically stable throughout the shelf life of the tablet.
3. It should be chemically stable throughout the shelf life of the tablet.
4. It should be compatible in nature.
5. It should be inactive in nature.
6. It should be effective in low concentration.
7. It should be nontoxic.
8. It should be non-irritant.
9. It should be non-sensitizing.
10. It should be stable for handling.
11. It should not have any interaction with drug.
12. It should be feasible.

## CLASSIFICATION OF ADDITIVES

1. Diluents; (fillers/bulking agents), e.g., Mannitol, sorbitol.
2. Binders; e.g., Methyl cellulose, polyethylene glycol.
3. Disintegrating agent; e.g., Sodium starch glycolate, powdered cellulose, microcrystalline cellulose.
4. Granulating agents; e.g., Starch, mucilage of acacia.
5. Lubricants; e.g., Titanium oxide.
6. Glidants; e.g., Silica, magnesium stearate.
7. Preservatives; e.g., Benzyl alcohol, sodium benzoate, benzalkonium chloride, parabens.
8. Antioxidant; e.g., Ascorbic acid, sulphate.
9. Flavoring agent; e.g., Ethyl vanillin, cocoa.
10. Sweeting agents; e.g., sucrose, sorbitol, Mannitol, aspartame, fructose.
11. Coloring agents; e.g., Tartrazine (yellow no. 5).
12. Solvent and co-solvent; e.g., Water, ethyl alcohol, polyethylene glycol (PEG), Diethylene Glycol (DEG).

 

13. Buffering agent; e.g., Acetate, phosphate, citrate.
14. Surface active agents/surfactants; e.g., polysorbates.
15. Ointment base; e.g., Mineral oil, wool wax, alcohol.
16. Coating agent; e.g., Phthalate, cellulose esters, cellulose acetate.
17. Sorbents; e.g., activated carbon, activated alumina.
18. Humectants; e.g., Salicylic acid, hyaluronic acid, urea, glycerin.
19. Chelating agents; e.g., Sodium thiocarbonate, EDTA.
20. Viscosity imparting agent; e.g., liquid Mannitol, sucrose, dextrose.

**Safety of additives**

1. Given that the toxicity of these excipients may vary from that of adults, it is unquestionably important to consider the safety of excipients used in pediatric goods [16, 17].
2. Developing approaches that offer a comprehensive evaluation of exposure to potentially hazardous excipients found in medications is crucial.
3. Identify the issues and difficulties surrounding the creation of pediatric formulations and think about how to get better medications and dose forms that are clinically appropriate for young patients.
4. Encourage the early evaluation of pharmaceuticals in the creation of pediatric medications.
5. Determine any possible gaps in knowledge and information while developing pediatric formulations.
6. Expand the knowledge from pediatric formulations that is available.
7. The pediatric Safety and Toxicity Excipients Database (STEP) was developed in response to the demand for convenient access to data about the toxicity and safety of the excipients.
8. The STEP database is offered as a data resource to make data on the use and acceptability of excipients in children easier to access. This enables a quick assessment of the risks associated with the use of specific excipients in the pediatric population and enhances the quality of scientific decision-making.
9. Detailed and comparable information about the acceptable and safe use of excipients in pediatrics may be found in the STEP database.

Pediatric medications used orally must be pleasant in order to promote dosage acceptance and regimen compliance. Reducing or removing the API's unpleasant qualities while taking into account its positive taste properties is one formulation technique for creating edible medication solutions. In many cases, taste masking is required to increase the API's palatability. Since the creation of pediatric medications may help people worldwide, taste masking should aim to achieve more than just a nice preparation's flavor [18]. The preparation should ideally have a flavor that is neutral and acceptable to the board's culture.

**NEW (NOVEL) Excipients**

The organization of the common technical documentation for the registration of pharmaceuticals for human use, ICH guideline M4, states that an excipient used in a drug product for the first time or via a novel mode of administration is considered new. Conversely, this guideline defines known excipients as “excipients that are well-established and commonly used in registered drug products and are usually included, have been used in pharmacopoeias” [19, 20].

There are many requirements outlined by US and European regulatory bodies for the use of an excipient in a pharmaceutical dosage form when it has not been used before. The IPEC New excipients assessment recommendations, dated October 1996, and the US FDA have both released guidelines about the safety testing necessary for novel excipients. These guidelines served as the foundation for the USP-NF 26 general chapter, excipient biological safety evaluation guidelines [21–25].

The information contained in these documents is useful for assessing the safety of a chemical for use as an excipient. The IPEC Europe safety committee has published a similar guideline. When creating a new or unique excipient, the manufacturer should create the safety documentation outlined in these recommendations according to the planned use of the excipient. This data serves as the foundation for

 

determining if the substance is appropriate for use as an excipient in a certain kind of dosage form. It is challenging to define "new" and "novel" with reference to excipients with precision. If an excipient is not included then it is obviously new.

- The FDA inactive ingredient database,
- Any of the three major compendia, US pharmacopeia (USP-NF), European pharmacopeia, or Japanese pharmacopeia (JP), or
- Other widely known compendia such as the "Handbook of pharmaceutical excipients". The industry recognizes that any change in the chemical composition of an excipient produces a new excipient, no matter how minor the modification to the chemical composition.

Mixtures of excipient ingredients can result in a novel excipient when the subject mixture is to be used in a dosage form for which its constituent excipients have not already independently been used in that intended route of administration. Physical modification of an excipient, such as micronizing or compaction does not generally produce a new or novel excipient. Nevertheless, co-processing can result in a palatable synergistic physical interaction between two or more excipients and provide special qualities that cannot be obtained by straightforward mixing. Compared to a new chemical entity, the safety evaluation for these co-processed excipients manufactured with widely existing pharmaceutical excipients would often be less demanding. The excipient is neither new nor novel if it is previously included in a pharmacopoeia or is used in other pharmaceutical dosage forms. In these cases, a thorough safety evaluation, as advised by the recommendations above, is not required [26–30].

## COMPENDIAL REQUIREMENTS

The additives must comply with the monograph requirements and the general notices. Verifying that an addition satisfies compendia standards in the area where the finished pharmaceutical product will be marketed is the user's duty. Throughout the world, several compendia are in use. The European Pharmacopeia (PhD. Eur.), the Chinese Pharmacopeia (Chp), the Japanese Pharmacopoeia (JP), the Japanese Pharmaceutical Excipients (JPE), and the United States Pharmacopeia-National Formulary (USP-NF) are the most often cited pharmacopeia. Compendia establish analytical specifications, test methods, and other attributes to demonstrate the quality of the articles used in pharmaceutical products.

In some instances, specific requirements may be included in a monograph when an additive is used for specific routes of administration. Additive and processing aids are commonly found in additive. The inclusion of these materials in compendia. As a result, it is advised that manufacturers of additives gather data on the identity, quality, and presence or potential presence of processing aids in additives. This is because their presence may affect patient safety, finished medicinal product testing, and stability.

It is recommended that additive producers verify that their products comply with the monograph standards listed in all relevant compendia before releasing them for worldwide distribution. Although there are ongoing initiatives to standardize additive monograph requirements in major compendia, these Compendia frequently have disparate monograph requirements. An additive must have been used on a medical product that has been approved in the relevant nation or area in order for it to be included in the USP-NF, Ph. Eur., JP, or JPE. Additionally, additives must be manufactured according to appropriate GMP to comply with compendia monographs. These expectations are described in the various Compendia.

### Certificate of Suitability (CEP)

Certificates of suitability are voluntary documents issued by the European directorate for the quality of medicines (EDQM). There are two types of CEPs:

1. One type demonstrates compliance to a Ph. Eur. Monograph.
2. The other type of CEP demonstrates of (TSE) Transmitting Transmissible Spongiform Encephalopathy. These CEPs are applicable to drug substances and additives, including those without a Ph. Eur. Monograph.

 

**International Pharmaceutical Excipients Council (IPEC)**

The makers, distributors, and consumers of additives created the International Pharmaceutical Excipients Council (IPEC), an international business group. In the Americas, Europe, Japan, China, and India, there are regional associations for the pharmaceutical additives sector. The goals of IPEC are to give best practices and advise on additive development, support the creation and harmonization of international standards for additives, and supply information helpful for the introduction of new additive development projects (Figure 2). IPEC has three major groups:

1. Additive manufacturers and distributors, defined as additive suppliers in this document.
2. Pharmaceutical manufacturers, defined as additive users in the document.
3. Public health and regulatory authorities.

## AIMS AND OBJECTIVES

### Aim

- To investigate and understand the regulations and standards that govern the development and use of Pediatric formulations.
- This includes examining the rules and guidelines set forth by regulatory bodies such as FDA and EMA, as well as any international standard that may apply.

### Objectives

The main purpose of this study is to:

1. Analyze the current regulatory landscape for a pediatric formulations and their additives, including any recent updates or changes in legislation.
2. Identify the specific requirements and consideration for developing and testing pediatric formulations, including dosage forms, safety and efficacy.
3. Evaluate the role of additives in pediatric formulations, including additives, flavors and colors and guidelines surrounding their use.

Understand the ethical considerations in prescribing and administering pediatric formulations, especially in terms of safety, dosing and patient acceptance.

## METHODOLOGY

Compendial Requirements for intended use of additives: There are three major compendia that are routinely referenced globally; the United States Pharmacopeia-National Formulary (*USP-NF*), the European Pharmacopoeia.

These compendia describe the quality of substances to be regularly used in pharmaceutical products, how to test them and the other general conditions required to assure the quality of pharmaceutical substances so that they are not harmful to the patient.

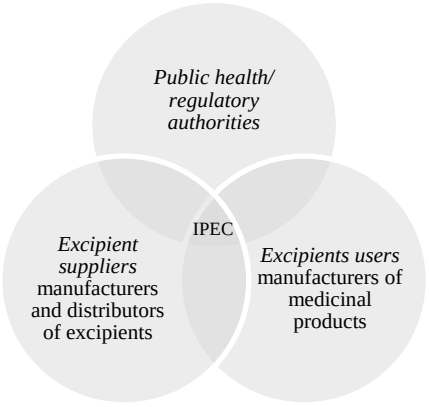


**Figure 2.** Major groups for IPEC.

 

The descriptions of substances for pharmaceutical use are called monographs and these list the analytical specifications and other quality attributes required to assure the safety and quality of the excipient. To market an excipient, there is no regulatory requirement that there must be a Compendial monograph for the material.

However, if a compendia monograph exists for an excipient in a particular region's pharmacopoeia, then the excipient should comply with that monograph because the regulatory authorities require conformance. However, other regulations may define a suitable quality which could be used (e.g., Food Chemical Codex).

Whenever possible, it is better to utilize a specification that satisfies a compendia monograph or a comparable standard rather than the supplier's internal document. In particular, the excipient already has an adequately specified quality for pharmaceutical use if it complies with a pharmacopoeia monograph, other pertinent general notifications, and compendia chapters.

In the United States, certain food additive materials are produced in conformance with the Food Chemical Codex (FCC). Many other national pharmacopoeias delineate the quality requirements of pharmaceutical ingredients, and these will take precedence over the three major pharmacopoeias. Where an excipient is described in a pharmacopoeia, the quality of material for pharmaceutical use must comply with this monograph (regulatory requirement).

The Compendial is concerned with the inclusion of processing aids and additives in excipients. The pharmacopoeias are currently debating this matter, although it is advised that excipient producers gather data on the types and amounts of additives and processing aids that are or may be included in their goods.

It is recommended that the manufacturer confirms that an excipient that is included in many compendia and might be sold internationally complies with the monograph requirements contained in each of those compendia. Even though there are significant efforts being made to reconcile excipient criteria with monographs in the three major compendia, one or more of these compendia now have requirements for monographs that differ from one another.

As a consequence, it is advisable to tabulate all monograph testing requirements from all compendia having an appropriate Monograph. Such a table should include the test name, specification range, and a brief explanation of the test methodology, as several compendial methods of analysis are frequently used. Following tabulation, the excipient provider can create a testing plan to guarantee compliance with every monograph specification found in the different compendia.

It would be satisfactory to validate the manufacturer's technique to show that it offers confidence that the excipient, when tested to each standard method, will conform to each monograph requirement where several test methods are cited for the same characteristic (attribute).

Before an excipient to be included in a monograph in the Ph. Eur., USP-NF, it must be commercially relevant and used in at least one authorized drug product. After a substance is used in a commercial pharmaceutical product, suppliers and users of excipients may request that their local pharmacopeia create a new monograph. In the absence of a pharmacopoeia or other compendia monograph, the manufacturers may create their own specifications using an already-existing monograph that is comparable.

**Based on Excess Addition of Additives in Active Pharmaceutical Ingredient**

Excipients are utilized in higher quantities overall than the active ingredient in a dosage form. Excipients, like medication ingredients, come from natural sources or are created artificially, chemically, or by some other method. Excipients were formerly thought of as inert components, but as time went on, researchers in the pharmaceutical industry discovered that excipients are actually rather active and may significantly affect dosage forms.

 

The performance of an excipient varies across batches from various manufacturers as well as from batch to batch within a single manufacturer. In pharmacological dosage forms, excipients nowadays are recognized to have well defined functional functions.

Their varied roles include controlling the APIs' solubility and bioavailability, improving the active ingredient's stability in the final dosage form, preserving the pH and osmolality of liquid formulations, and serving as lubricants, diluents, disintegrants, aerosols, emulsifying agents, and antioxidants.

Additionally, excipients interact with the active ingredient in the formulated dosage form and generate a matrix that can influence important drug substance quality properties including bioavailability and stability. Excipients may have an impact on the final dose form; they may also have an impact on a product's safety and effectiveness. Excipients are therefore something that pharmaceutical companies need to carefully examine when adding to a dosage form.

**CASE STUDY 1: DEG (DIETHYL GLYCOL)**

The global DEG market is projected to grow from 2.6 million metric tons in 2020 to 3.44 million metric tons by 2026 at a CAGR of 4.8%. Due to growing government investments in infrastructure development and fast industrialization, especially in China and India, the Asia Pacific area is predicted to experience tremendous growth. DEG has various uses, including as a raw material for polyester resins and plasticizes, a humectant, dehydrating agent in natural gas, plasticize for paper, and as demulsifies and lubricant. The market is divided into two main segments: the end-use industry, which includes the agrochemical, automotive, cosmetic and personal care, paints and coatings, oil and gas, textiles, and plastics industries; and the application, which includes antifreeze and coolant, solvents, humectants, polyester resins and plasticizers, emulsifiers and lubricants, and others (Figure 3).

By the growing demand for plasticizers in the plastics industry, as well as its extensive use in personal care and cosmetics products. The global DEG market is projected to grow at a CAGR of 4.8% from USD 163.79 billion in 2022 to USD 400.43 billion by 2030. DEG is a colorless, low viscosity liquid that dissolves fully in water, alcohol, organic solvents, and acetone. In the printing, paint pigment, and textile industries, it serves as a solvent.

It is also used as a raw ingredient in the manufacturing of various products, including plasticizers, polyester resins, and thermoplastic polyurethanes. The market’s growth drivers include increased demand for cement and paints, while the toxic nature of DEG and patent registrations pose a restraint to its growth. The Asia-Pacific region holds the largest market share due to the increasing demand for various end-user industries such as building and construction, chemicals, and the automotive industry.

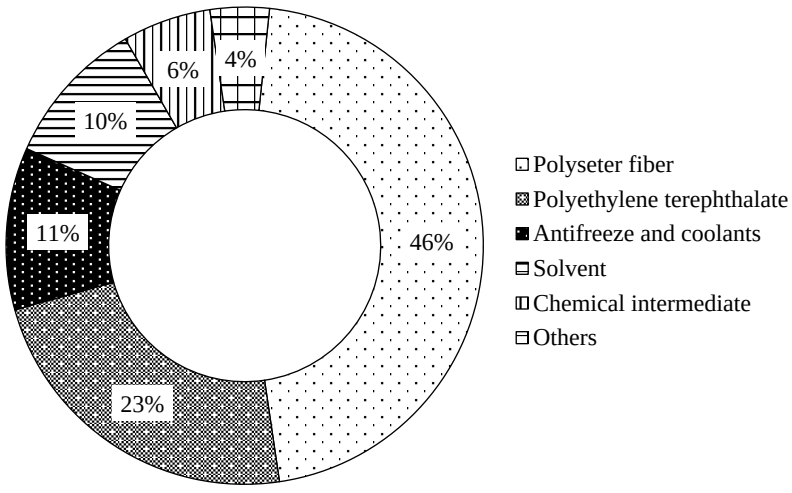


**Figure 3.** Diethylene glycol along its proportion.

 

**Case Study (A)**

The first and most notorious mass poisoning was of sulphanilamide contaminated with DEG termed as the Massenet disaster in America in 1937. DEG (72%, v/v) was used as solvent in the sulphanilamide elixir. No toxicity tests were performed on either the pre-marketing ingredients or the final products. Shortly thereafter, it was distributed in the United States. Mainly, the products were distributed in the southern states, where adverse effects and deaths were recorded. A total of 353 patients were hospitalized and 105 out of these patients died (34 children and 71 adults). The United States Federal Food, Drug, and Cosmetic Act of 1938 was created as a result of this catastrophe, requiring the safety of drug products to be approved before they are sold. When seven youngsters in Cape Town, South Africa took over-the-counter sedatives (Plexin or Proknapp) in 1969, their kidneys failed them owing to poor quality. Five patients in a Spanish burn unit in 1985 had anuria while receiving treatment. All patients received topical silver sulfadiazine ointment treatment, according to a later inquiry, however despite receiving treatment, the patients passed away from renal failure. The reason was due to 6.2–7.1 g/kg DEG contamination in the ointments. DEG is hardly absorbed in its normal form. Suspected skin and systemic toxicity were due to the combination of the wide range of treatments, repeated use of the product and the damaged skin of the patients.

21 patients (from two separate incidents) died of renal failure in India after administering industrial glycerin (18.5%, v/v, containing DEG) as part of their treatment. In summer of 1990, 47 children were admitted to Josh University Teaching Hospital Nigeria, who later developed kidney failure and lost their lives. All were given syrup contaminated with DEG which was used to replace propylene glycol. A similar case where 236 children died from this painkiller contamination was seen in Dhaka, Bangladesh between 1990 and 1992.

**Case Study (B)**

In Argentina, around 1992, 29 people died of Propolis syrup contamination, and it was only found that the amount of DEG in it ranged from 24.00 to 66.5%. In 1996 in Port-Au-Prince, Haiti, 88 of the many young infants were confirmed dead because of contaminated paracetamol. In 1998, 36 children developed acute renal failure after the intake of a cough expectorant manufactured in Gurgaon, India, and 33 of those children died despite receiving peritoneal dialysis and supportive care. Epidemiological investigations found that the drug contained 17.5% contamination of DEG. In Panama in 2006, there was an official estimate of 78 deaths, and these resulted from unexplained renal failure with neurological dysfunction. Later, it was discovered that it was a cough syrup which was contaminated with an average of 8.1% DEG. The syrup was manufactured from glycerin imported from China through a European broker.

And the resulted cough syrup was found to be contaminated with an average of 22.2% DEGs. In the same year that meant another outbreak in China near 2006, 12 patients died from administration of contaminated armillarioid. In 2008, 84 children died in the country of Nigeria between November and December after ingesting teething syrup contaminated with DEG. DEG was added to give a sweet taste to Austrian wines. Consumption of this alcohol caused acute renal failure. 41 fake toothpastes found in the United Kingdom contaminated with DEGs were found in some other countries also, but no serious illness was reported from the use of these adulterated toothpastes.

**CASE STUDY 2: EG (ETHYL GLYCOL)**

EG when enters the human body gets metabolized by an enzyme, alcohol dehydrogenase to form intermediary products glycolic and oxalic acids. Glycolic acid causes metabolic acidosis whereas glycolate inhibits cellular respiration. In some patients, the metabolism of EG was observed to contribute to the development of lactic acidosis. Calcium oxalate, resulting from oxalic acid and calcium, may cause acute renal failure, neurological function, myocardial dysfunction, and pulmonary dysfunction. Deposition of calcium oxalate in tissues also causes hypocalcemia, which suppresses cardiac function and BP.

 

**Case Study (A)**

In 2019–2020, some people in the Brazil, Belo Horizonte city from a small upscale brewery, drank a brand of beer containing an amount of DEG that initially caused symptoms such as, acute kidney failure, vomiting, abdominal pain, and blurred vision. Later, temporary blindness began to occur, and fatalities were reported from this tragedy.

The police found that the beer caused the deaths due to its contamination with diethyl glycol and its high concentration. In the first week of 2020, about 17 children were admitted to a hospital in Rama Nagar, Jammu and Kashmir, India, who took Cold best PC cough syrup as medicine and a batch of this cough syrup contained 34.97% of DEG.

More than half of these children died of kidney failure. In October 2022, the WHO issued a medical product alert for four "contaminated" Indian pediatric drugs manufactured by Maiden Pharma in Sonipat, Haryana, India.

The WHO stated that unacceptable amounts of DEG and EG have been found to be contaminated. The samples of each of the four products were confirmed by laboratory analysis by the WHO. In Gambia, 66 children died, later the death rate increased.

**CASE STUDY 3: TALCUM POWDER**

The most common cosmetic applications for talc are face, body and baby powders, but it is also used as an ingredient in color cosmetics, soap, toothpaste, antiperspirant, chewing gum and drug tablets. Talc, also known as talcum powder, is a naturally occurring mineral that is highly stable, chemically inert and odorless.

The grade of talc used in cosmetics is of high purity comparable to that used for pharmaceutical applications and it is only mined from select deposits in certified locations before being milled into relatively large, non-reparable-sized particles.

**Case Study (A)**

Asbestos used as an additive in baby powder. The long period usage of baby powder containing talc, it has been reported that it causes a serve damage of private parts of babies, so, the usage of talc as additives has been recruited by the government of India. Instead of talc in baby powder, it is replaced by corn starch.

**CASE STUDY 4: HEPARIN**

Heparin is an anticoagulant that prevents the formation of blood clot. Heparin is also used before surgery to reduce the risk of blood clots.

**Case Study (A)**

In January 2008, a case has been reported against a heparin used in dialysis conducted in pediatric resulted in allergic reactions, hypotension, tachycardia, urticarial, and facial edema occurring almost immediately after starting dialysis. In 2008, Chinese heparin adulteration, refers to heparin adulteration incidents that occurred in the United States of America in 2008. Baxter then sold this adulterated heparin in the US, which killed 81 people, and left 785 severely injured.

## MAJOR COMPENDIA

### United States Pharmacopeia and National Formulary

The USP and NF are legally separate compendia officially mandated in the US federal food, drug and cosmetics act. So, they are published together in a single book. To be considered for inclusion in the USP-NF, a new additive should have been used in an approved drug product or be listed in another pharmacopoeia. A monograph is prepared for the new additive with input from both the additive

 

manufacturers and pharmaceutical users. The draft monograph is then published for comment in the Pharmacopeia Forum and then submitted to the USP for approval. The USP-NF includes a General Information Chapter which elaborates on the GMP requirements for producing an additive.

The USP-NF also specifies the requirements for properly testing an additive both in terms of the requirements for validated test methods as well as by detailing specific test methodology. Generally, additive monographs (specifications) are contained in that portion of the USPNF called the National Formulary (NF) unless they also have been used in a dosage form where they function as the Active Pharmaceutical Ingredient (API), in which case they are contained in the United States Pharmacopoeia (USP).

The monographs detail the test methods and specification limits which must be achieved in order to market an additive as compendia grade. Certain monographs also contain additional information such as labeling and storage requirements.

**European Pharmacopoeia**

The new ingredients that Pharmaceutical European will be receiving, it has to be a non-collectable part of a previously authorized pharmaceutical product. The member state or states to which the application has been filed evaluate and approve the drug product made with the new addition components, to be added to the pharmaceutical European market after being utilized in an authorized medicinal product.

The European Pharmacopoeia Commission's work program needs to incorporate the new additions. The secretariat will identify the additive makers, and the additive is typically allocated to an expert group. After receiving specifications, test procedures, and samples from the additives' providers, the expert panel will create a monograph that will be available for public review, published in Pharmaceutical European, and approved by the European Pharmacopoeia Commission. Following Commission clearance, the additive is included in European medicinal products.

**cGMP (current Good Manufacturing Practice)**

For additives used in pediatric formulations, the International Council for Harmonization of Technical Standards for Pharmaceuticals for Human Use (ICH) has established good manufacturing practices (GMP) criteria. These suggestions for the identification, qualification, and management of possible contaminants in additives are known as ICH Q3D guidelines.

The producer of the additives must be able to show proof of adherence to GMP guidelines for the manufacturing and management of the additive, under ICH Q3D. Assuring the appropriateness of the facilities and equipment used in production, maintaining a quality management system, and accurately documenting the production processes are all part of this.

Additionally, the producer has to have policies in place to keep an eye on and regulate the quality of the raw materials used to make additives. This entails checking the materials for impurities and testing them, as well as putting in place a mechanism to recognize and handle any possible dangers connected to using the additive.

ICH Q3D also recommends that the manufacturer of the additive should have a comprehensive system in place for the qualification and control of impurities. This includes conducting risk assessments to identify potential impurities, setting specification for impurity limits, and implementing appropriate control measures to minimize or eliminate impurities. The manufacturer should have a process in place for conducting stability studies on the additive, in order to determine the shelf life and storage conditions of the product. The guidelines set forth by ICH Q3D aim to ensure that additive used in pediatric formulation is of the highest quality and suitable for use in these sensitive populations.

 

Manufactures are encouraged to adhere to these guidelines to ensure the safety and efficacy of pediatric formulations.

**GMP and Quality Standard for Additives**

Additives industry, which consist of hundreds of small companies faced with a strict regulatory framework, increasingly demanding quality standard and a customer base that expects added but increasingly improved services.

No study is required if the drug product's mode of administration necessitates high GMP and contains the primary ingredients. If not, the additive's nature and manufacturing process must be evaluated as they may raise the necessary GMP level.

Because of their intrinsic nature, additives must be produced with regard for their usefulness as additions in medicinal products, as well as for their potential to cause toxicity and cross-contamination during manufacture. This inherent nature of additive can raise the requirement for GMP compliance.

**GLP (Good Laboratory Practice)**

Recommendations for nonclinical testing of additives or excipients meant for use in pediatric medication products are provided by the ICH guidelines for the Good Laboratory Practice (GLP) of additives or excipients in pediatric formulations. The recommendations are intended to guarantee these items' quality and safety for patients who are younger.

These guidelines emphasize the need for nonclinical studies to assess the potential risks and benefits of additives or excipients in pediatric formulations. The studies should be conducted using appropriate animal models and should include evaluations of pharmacokinetics, dosing, and toxicology. The guidelines also recommend conducting these studies in a step-wise manner, starting with small-scale studies and then progressing to larger studies if necessary.

In addition to nonclinical studies, the guidelines also address the need for thorough characterization of the additives or excipients, including physicochemical properties, stability, and compatibility with the drug substance. The guidelines stress the importance of quality control and consistency in the manufacturing process of these additives or excipients.

Overall, the ICH guidelines for GLP of additives or excipients in pediatric formulations provide a framework for the assessment and evaluation of these components in pediatric drug products. By following these guidelines, manufacturers can ensure the safety.

## RESULT

**Case Study 1 and 2**

Because of their advantageous physical and chemical characteristics, DEG and ethylene glycol (EG) are often used excipients in medicines, cosmetics, and other industrial applications. However, there are a lot of obstacles to their use because of their toxicity and contamination potential.

There are many such solvents which are used for manufacturing drugs that may prove to be lethal in case of no quality check by the quality control personnel. DEG has been responsible for large-scale poisoning outbreaks that have claimed many lives one way or another.

DEG, is usually associated with contaminated medicines. Because of these epidemics, about 1 ml/kg of body weight (perhaps much less) is thought to be a lethal dose for some people. Therefore, it is crucial to establish appropriate quality control measures, including rigorous testing and monitoring, to ensure their safe use. In addition, alternative excipients should be explored and developed to mitigate the risks associated with DEG and EG usage.

 

To guarantee product safety and efficacy and to make well-informed decisions, it is important to have a comprehensive comprehension of the constraints and difficulties associated with the use of DEG and EG as excipients.

**Case Study 3**

69% of parents said they regularly use baby powder to take care of their infants' skin. During standard well-child checkups, a survey of 100 parents of children between the ages of 2 weeks and 6 months was conducted to find out how much the parents knew about baby powder.

The hospital should determine the policy of providing a free powder sample to newly delivered mothers. The baby powder has ability to kill bacteria and yeast and to prevent diaper rash less than 0.01%. The usage of baby powders for a short term and long term creates harmful effects on the private parts of the new born babies.

**Case Study 4**

Heparin prophylaxis in medical and surgical patients at risk of venous thromboembolism is safe and effective when administered at a modest dose of 5000 USC every 8 or 12 h. At low dose, heparin reduces the risk of venous thrombosis. The use of heparin for more the 5 to 6 days is associated with rare risk of thrombocytopenia. The heparin should be injected at the preferred site (abdominal area).

## REGULATORY ASSESSMENT

When considering whether to introduce an addition to the pharmaceutical market, prospective additive makers should consider a number of safety-related factors.

First, it is important to determine if the substance has already been used in pharmaceutical products or in applications comparable to them, including medication additives or drug contact package components. The safety of the substance may already be suitable for possible usage as an addition in the pharmaceutical business if a history of use in applications involving human exposure can be demonstrated.

The Food and Drug Administration (FDA) in the United States has an additive database. Since the inactive ingredients database (IID) records every additive that has been permitted due to its inclusion in an approved innovative drug product, it should be utilized to determine the order of usage. Each ingredient is given with its name, dosage form, and the highest quantity that may be found in a medicine that has been authorized and uses that dosage form. It is important to take caution while searching the database since other names for additives might appear, such as commercial name, chemical name, compendium name, or general description (for tastes and dyes). Europe does not have a multinational list of additives used in approved medicinal products. So, in order to establish precedence of use, it is necessary to review national medicinal.

## CASE STUDY RESULTS SHOULD FOLLOW THE GUIDELINES

### USFDA: United States of Food and Drug Administration

Specific standards on the use of additives in pediatric goods are set out by the US Food and Drug Administration (FDA). These recommendations guarantee these items' efficacy and safety for kids. Among the important rules are:

- *Safety:* All additives used in pediatric goods must be deemed safe by the FDA for use in children. Additives need to be thoroughly tested to make sure kids cannot get hurt by them.
- *Dosing must be done correctly:* Additives used in pediatric goods need to be dosed for little children. This indicates that the product's additive concentration has to be appropriate for the weight and age of the child.
- *Recommendations based on age:* The FDA suggests that the additives used in pediatric goods be tailored to the age of the user. This implies that the kind and amount of the additive may change based on the child's age.

 

- *Labeling requirements:* Children's goods with additives must have accurate labels, according to the FDA. The product's recommended age range, along with any particular dosage guidelines or safety measures, must all be made crystal apparent on the label.
- *Efficacy:* Additives used in pediatric products must be shown to be effective in treating or preventing the condition for which they are intended. The FDA requires manufacturers to conduct clinical trials or provide scientific evidence to support the effectiveness of their products.

Overall, the FDA's guidelines for pediatric additives aim to ensure the safety and effectiveness of these products for children. These guidelines help to protect the health and well-being of children by ensuring that the additives used in pediatric products are appropriate and beneficial.

**ICH: International Council of Harmonization**

***Regulatory Compliance***

Manufacturers are required to abide by applicable local, national, and international laws, rules, and recommendations. Examples of these include directives from the European Medicines Agency (EMA) in the European Union and the Food and Drug Administration (FDA) in the United States.

***Facilities and Equipment***

To prevent contamination and guarantee product quality, manufacturing facilities should be planned, run, and maintained. For the handling and processing of additives, suitable apparatus such as mixing vessels, pumps, and filtering systems should be employed.

***Personnel and Training***

It is important to make sure that workers who handle, manufacture, and test additives are well trained so they have the know-how to do their jobs well. Training on GMP concepts, hygienic procedures, and managing hazardous products are all included in this.

***Record-keeping and Documentation***

Manufacturers need to have systems in place for properly documenting every step of the production process, including batch records, processes, and requirements. It should be simple to obtain these documents for auditing and evaluation.

***Quality Control***

To make sure each batch of additives satisfies the necessary requirements and standards, sufficient quality control tests should be carried out on them. Identification, purity, potency, and other pertinent factors are tested for in this process.

***Documentation and Release of Batches***

Before any batch of additives is released for distribution, it should undergo a thorough review, including all relevant testing and documentation. Only batches that meet the established specifications and standards should be released.

***Traceability***

Sufficient mechanisms have to be set up to monitor the movement of additives from the procurement of raw materials to the distribution of finished goods. This guarantees that the cause of any quality problems or recalls may be identified.

***Stability Testing***

Manufacturers should conduct stability testing on the additives to ensure their shelf-life and storage conditions that are suitable for maintaining their quality and efficacy. This includes testing at different storage temperatures and time points.

 

***Labeling and Packaging***

Adhesives must be packaged and labeled in accordance with all applicable laws and policies. This covers the labeling of component lists, dosage guidelines, and any relevant cautions or warnings in an accurate and understandable manner.

**Regulatory Approach for Pediatric Drug Development**

*Step 1:* Understand the definition of pediatric population.

⇩

*Step 2:* Understand the prevalence, age distribution and mechanism of disease in pediatric population.

⇩

*Step 3:* Understand the pediatric regulatory legislation globally.

⇩

*Step 4:* Define the strategy and timelines for pediatric vs. adult clinical studies.

⇩

Step 5: Take scientific advice or meeting with HA, if needed.

⇩

*Step 6:* Submit and agree pediatric development plan -PSP (in US) or PIP (EU) to HA.

⇩

*Step 7:* Conduct the relevant preclinical and clinical studies and submit the relevant data to HA.

⇩

*Step 8:* Receive the approval for pediatric use.

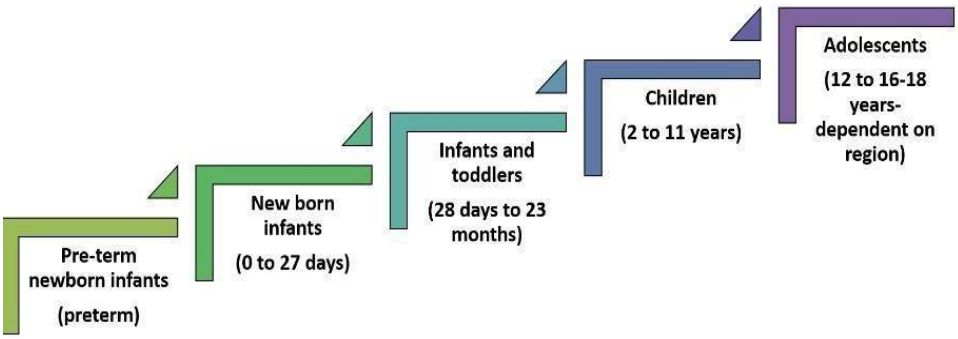


**Figure 4.** Steps required for regulatory approval.

**Summary**

The safety, effectiveness, and proper administration of medications for children are the main goals of the regulations governing pediatric formulations and additives. When it comes to treating the special physiological and developmental traits of pediatric patients, these recommendations are essential. Key considerations include dosage forms, safety profile, and age appropriate formulations.

**Regulatory Framework**

- Regulatory agencies, such as the FDA and EMA, have specific guidelines for pediatric drug providing benefits to pediatric population (Figure 4).

 

**Age Appropriate Formulation**

- Tailoring formulations to different age groups, considering factors like taste preferences and ease of administration.
- Guidelines often specify dosage forms suitable for specific age ranges, such as liquids for infants and chewable tablets for older children.

**Dosage Precision**

- Stringent requirements for accurate dosing to prevent under or overdosing.
- Pediatric formulations may involve a range of strengths to accommodate diverse age groups and weight categories.

**Safety and Toxicity**

- Thorough assessment of potential toxicity and adverse effects in pediatric populations.
- Strict monitoring of additives to ensure they are safe for children.

**Palatability and Acceptance**

- Consideration of taste, smell, and overall palatability to enhance medication adherence in children.
- Development of flavorings and masking agents to improve the acceptability of formulations.

**Pediatric Pharmacokinetics**

- Understanding age related changes in drug absorption, distribution, metabolism and excretion.
- Formulations designed to accommodate differences in this pharmacokinetics parameters.

**Clinical Trials**

- Requirements for pediatric specific clinical trials to establish safety and efficacy.
- Incentives for conducting pediatric studies to address the lack of data for many drugs used by children.

**Labelling and Packaging**

- Clear and comprehensive labeling to provide information on dosage, administration and potential risks.
- Child resistant packaging to minimize the risk accidental ingestion.

## CONCLUSION

Preclinical study is very important to know about the safety and efficacy because pharmaceutical additives are no longer considered as inert substances. New Drug Development involves a range of preclinical studies to show efficacy and safety to support clinical trial work; and product licensing safety studies include absorption, distribution metabolism, excretion, Pharmacokinetics, non-toxicity, and carcinogenicity investigations within industry.

Nowadays, the use and safety of additives established is given importance in new drug development process. In excipient development, main aspects considered are chemical, manufacturing and preclinical data. The absence of worldwide rules for the safety evaluation of additions, an authorized additives list, and a preclinical assessment approach all have an impact on preclinical assessment in the creation of additives. Additives are not inert materials as was previously thought.

Additives must first undergo preclinical testing before being included in a formulation since they may have unfavorable toxicological reactions whether used alone or in combination with other drugs. Additives induce a variety of undesirable effects, such as hypersensitivity, allergies, or anaphylaxis nature, rather than performing various useful tasks in a medicine composition.

Preclinical research is particularly crucial when it comes to new additives. Substances emerging from a structural alteration of a "approved" food additive, a recognized food additive, a structurally modified

 

food additive, or a component of an over-the-counter (OTC) medication are examples of new additions from an intermediate category. However, in accordance with recommendations created by the Centers for Biologics Evaluation and Research (CBER) and Drug Evaluation and Research (CDER), the term "new additives" refers to any inactive ingredient added to therapeutic and diagnostic products internationally that is thought to have no therapeutic effect at the intended dosage, although they may act to improve product delivery (e.g., enhance absorption on control release of drug substance) and are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration. This is in accordance with "Guidance for the industry nonclinical studies for safety evaluation of pharmaceutical additives".

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