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MINISTRY OF HEALTH OF UKRAINE
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QUALIFICATION WORK

on the topic: ANALYSIS OF REQUIREMENTS OF REGULATORY DOCUMENTATION OF DIFFERENT COUNTRIES REGARDING THE COMPOSITION OF PEDIATRIC MEDICINES

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ANNOTATION

The qualification thesis provides an analysis of the requirements of the regulatory documentation of different countries regarding the composition of pediatric medicinal products. According to the literature, the requirements for the use of excipients included in pediatric medicinal products have been established. The work, laid out on 45 pages, contains 4 tables, 3 figures, and 73 references.

Key words: pharmacopoeia, requirements, pediatric drugs, excipients..

АНОТАЦІЯ

У кваліфікаційній роботі наведено аналіз вимог нормативної документації різних країн щодо складу педіатричних лікарських засобів. За даними літератури встановлено вимоги щодо використанні допоміжних речовин, що входять до складу педіатричних лікарських засобів. Робота, викладена на 45 сторінках, містить 4 таблиць, 3 рисунки, 73 посилань.

Ключові слова: фармакопея, вимоги, педіатричні препарати, допоміжні речовини.

CONTENTS

INTRODUCTION

Actuality of topic. An Active Pharmaceutical Ingredient (API) is the term used to refer to the biologically active component of a drug product, while an excipient is often defined as an inactive substance that serves as the vehicle or medium for a drug or other active ingredient. This often leads to the misunderstanding that an excipient is an inactive ingredient. That excipient can be referred to as inactive appears to derive from the fact that they are seen solely as ingredients used to produce a tablet, cream or solution that allows a patient to receive the API. However, excipients often perform vital and active roles in medicines, including:

- helping to control the bioavailability of an API to meet specific requirements
- assisting with binding and coating in the drug manufacturing process
- performing a critical role in stabilising unstable components such as proteins
- the use of colourings and flavourings to mask unpleasant tastes or odours and allow easy identification of different drugs.

Perhaps some of this misconception or poor terminology comes from the fact that excipients are often not initially developed and manufactured to be used by the pharmaceutical industry – the origin of excipients are often in another industry altogether. For example, a material designed and developed primarily for the automotive industry may have the right characteristics for use in a pharmaceutical product. The safety data, specifications and testing requirements for the material may be perfectly sensible for use in the automotive industry, but it should not be taken for granted that these would be sufficient for its use in a medicinal product. Whilst the primary component could be known to be safe, consideration must also be given to the related impurities that may be the result of the manufacturing process.

The aim of the master's thesis was to study the requirements of national pharmacopoeias for pediatric drugs. Namely, the use of auxiliary substances in their

composition. To complete the master's work, it was necessary to complete the **following tasks:**

- literature analysis regarding the technology of pediatric drugs;
- establishing the requirements of national pharmacopoeias for pediatric preparations;
- characterization of excipients used in the technology of pediatric preparations.

Implementation of results. The main provisions of the qualification work are set out and discussed in the 3rd International scientific and practical conference “"Current Issues of Medical-Biological and Pharmaceutical Sciences"” (Marth 30, 2023, Zhytomyr).

Structure and scope of qualification work. Qualification work consists of an introduction, literature review (Chapter 1), the experimental part (chapter 2 and 3), general conclusions, references, appendixes. The work is presented on 45 pages, includes 4 tables, 3 figure, 73 sources of literature.

CHAPTER I

PEDIATRIC DRUG FORMULATIONS: A REVIEW OF CHALLENGES AND PROGRESS

1.1 Modern approaches in the development of children's medicines. The neonatal and pediatric populations have long been neglected concerning the development of oral dosage forms. For close to two decades, caregivers have had to adjust the doses of the off-label medicines and drugs for adults to suit the neonatal and pediatric needs. This is due to the lack of rules and regulations regarding neonates and pediatrics clinical trials while pharmaceutical industries see this as a non-lucrative approach. Despite such limitations, the administration of solid and liquid dosage forms to neonates and pediatrics necessitates the development of new technologies and even new strategies to meet the needs. Current approaches have not only focused on the development of suitable dosage forms but also the advancement of devices to enhance drug administration to pediatrics and neonates. Though current approaches have significantly added to the number of pediatric and neonatal oral dosage formulations on the market, there is still more room for improvement(s). While novel dosage forms including multiparticulates, orodispersible tablets/films, and chewable tablets have extensively been researched, some administration devices (e.g., nipple shield, pill swallowing cup, and solid dosage pen) have also been explored. Although a few of these products are in the market, the concerted efforts of regulation administrative bodies, pharmaceutical industry settings, and scientists in academia have been oriented to address all issues and advance the neonatal and pediatric-centric pharmaceutical products.

Oral or peroral drug delivery refers to using mouth as a port of drug entry to the body that is intended for local or systemic drug absorption, and despite its challenges it is widely accepted by a broad range of populations and in many

countries. Although oral dosage forms have taken large portion of the drug market, other routes of drug delivery including pulmonary, transdermal delivery systems, and nano-systems are expected to show promising leap in the future market. Oral dosage forms can simply be supplied as liquids, dispersed systems, and solids but can also be equipped with proprietary technologies to deliver the drug as intended.

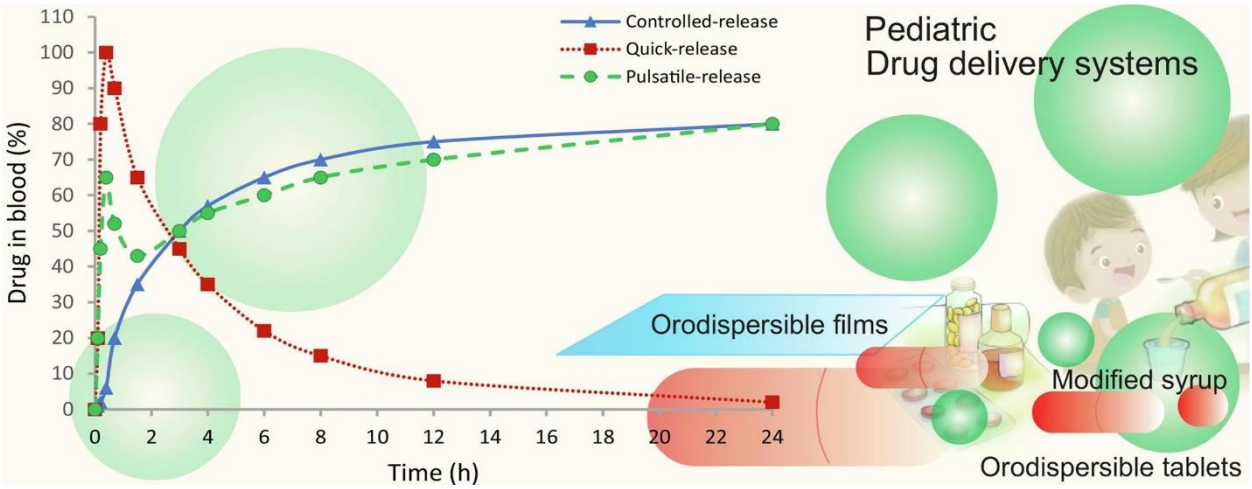

Figure 1.1 Properties of pediatric medicinal products

Although solid, dispersed, and liquid dosage forms are administered orally, the former is preferred due to stability and convenience for patients to carry around. Pediatric patients, however, due to their incomplete and continuous organ development may require different oral drug delivery systems (DDSs) assisted with its special dosing and administration requirements. Since most pharmaceutical industries consider the pediatric and neonatal drug market as not lucrative and attractive, they primarily target the adult population. This leaves the pediatric and neonatal population with no option but to be served with the adjusting and compounding of the adult dosage forms, which has become a common practice. In fact, a collaborative effort from researchers and manufacturers is required to develop age-appropriate oral DDSs that are pediatric-specific. Such an outlook may also pave the way towards the production of novel DDSs to benefit geriatric patients to

surmount the age-related impaired physiological, visual, motoric functions, and swallowing difficulties.

1.2 Major Challenges to Be Considered in Pediatric Formulation Development and Approaches to Overcome the Challenges

Quality, efficacy, and safety of the final drug product have been the main challenge in developing age-appropriate pharmaceutical formulations. Particularly more challenging is the development of pediatric formulations in comparison with that of adults largely because of some differences in physiologic functions and additional demands of this target population. For any given drug, apart from the pharmacokinetic (PK) and pharmacodynamic (PD) profiles, special attention is essential to suit the dosing requirements for all age groups with great flexibility. In the past, manipulations of adult dosage forms (e.g., crushing tablets and mixing with juice; breaking tablets into smaller parts) have been the “go-to method” to serve neonates and children. In recent years, however, the main focus has been based on the development of novel technologies for the preparation of age-appropriate formulations, with modifications in the regulatory framework as additional incentive force.

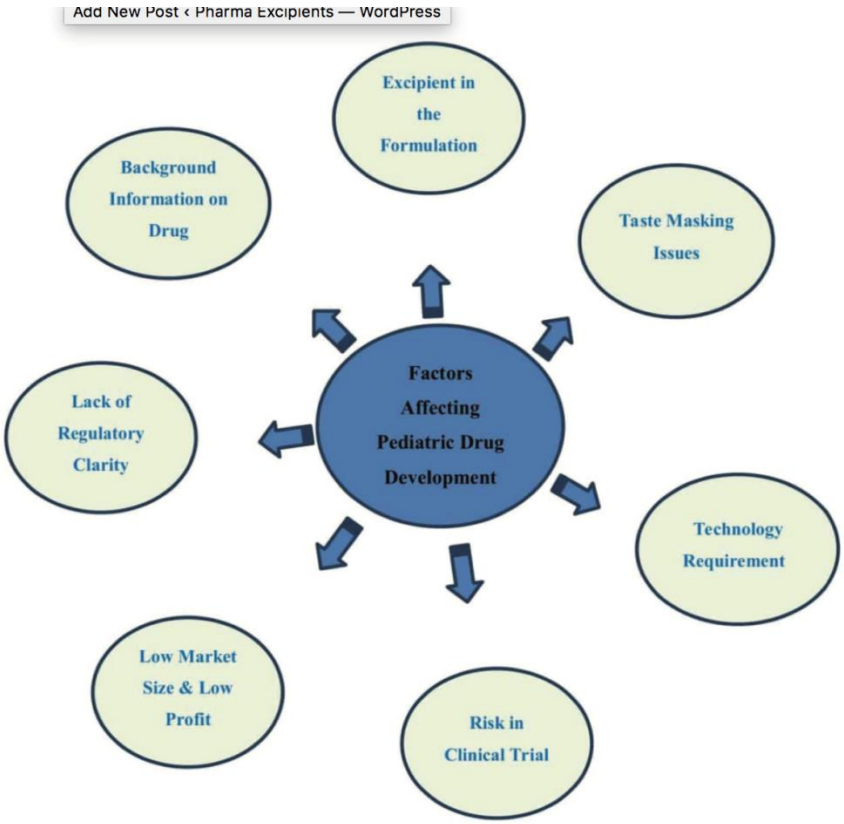

Figure 1.2. Pediatric dosage forms—challenges and recent developments

The future looks promising with an increased number of researches focused on the novel means to meet the needs of neonatal, pediatric, and even geriatric populations. In this review, we discuss the past and current neonatal/pediatric drug delivery approaches and delve into hurdles and hopes concerning developing age-appropriate formulations.

Child-appropriate drug formulations are required for efficient and safe therapy of diseases in childhood. Children have different needs and requirements compared to adults. Due to the continuously varying characteristics of the juvenile organism during physiologic and cognitive maturation, the pediatric subpopulations are an inhomogeneous collective. Various authorized and often used medicines do not adequately reflect the needs of children.

In general, child-appropriate drug formulations have the following key attributes:

–Sufficient and predictable bioavailability and efficacy of the active pharmaceutical ingredient

–Toxicologic safety of all components (including the excipients)

–Correct and precise drug dosing (acceptable dose uniformity)

–Acceptable properties (palatability, handling, etc)

–Sociocultural acceptability (missing stigmatization)

–Precise information on safe handling and administration of the medicine

- “Child-proven” packaging.

As the preferred and predominant route of administration is the oral route, the next sections will focus on the oral route of administration.

Table 1.1

Major Challenges to Be Considered in Pediatric Formulation Development and Approaches to Overcome the Challenges

Challenges	Approaches to Overcome the Challenges
Dose heterogeneity/ precise dosing	Technology platforms enabling flexible dosing: Liquid formulations Multiparticulate formulations Use of medical devices for partitioning or accumulation of doses
Low doses required	Industry: Carefully chosen and validated blending process Control of drug adhesion to surfaces Granulation before tabletting Drug printing (in future) Pharmacy: Extemporaneous liquid formulations Use of stock solutions/blends

	Magistral preparations preferred Compounded capsules, powders, suppositories
Limited swallowability	Solid technology platforms facilitating swallowing: Orodispersible dosage forms Multiparticulate fomulations Mixing with food (has to be validated)
Lacking adherence because of a bad taste	Taste-masking technologies: Functional coatings for barrier formation Complexing API, eg, by ion exchanger Increasing viscosity Early involvement of taste assessment in development Animal models Electronic tongues Adult taste panel (if appropriate)
Lack of understanding of medicine related topics	Designing the dosage form as child-friendly as possible Self-explaining administration, eg, X Straw® Printed motives on drug dosage forms
Toxicity of ingredients in subpopulations, eg, neonates	Careful risk assessment for each component Toxicologic databases (STEP database) Avoid excipients with unclear safety in target population, eg, preservatives

CONCLUSIONS

Pediatric drug products require specialized consideration in formulation development. Recent changes to US and European regulatory requirements for pediatric drugs have transformed what once was only a niche area to an important field in drug development.

It has been established that there is an urgent need for pharmaceutical products tested and approved as safe and effective for use by children. From 1973–1997, the percentage of approved drugs that did not contain any pediatric labeling information remained fairly stable at 71–81%. Of the 33 new molecular structures approved in 1997, 27 had potential for pediatric use, but only nine contained any pediatric labeling information (2). Two-thirds of drugs currently prescribed to children have not been studied or labeled for pediatric use.

EXPERIMENTAL PART

CHAPTER II

ANALYSIS OF REQUIREMENTS FOR EXCIPIENTS OF PEDIATRIC DRUGS

2. 1 Mandatory requirements for pediatric drug development in the EU and the US for novel drugs

In the past, medicinal products were rarely evaluated in the pediatric population, resulting in a scarcity of drugs approved for use in the pediatric population, resulting in a high level of off-label use in this population. Since market forces have not been able to drive changes, initiatives have been implemented in several regulatory regions to support the establishment of knowledge on how to use medicinal products in the pediatric population [15]. However, the European Union (EU) and the United States (US) were the first regions to introduce mandatory pediatric legislations [16].

The US Pediatric Research Equity Act (PREA) made the inclusion of the pediatric population (from birth to the age of 16 years) mandatory during drug development when it came into force in December 2003 [17]. It complemented the already existing voluntary Best Pharmaceuticals for Children Act (BPCA) implemented in 2002 [18] where a reward could be gained for the conduct of requested pediatric drug development. The EU Pediatric Regulation adopted in December 2006 was built upon the learnings from the US [19] and combined mandatory requirements with rewards as incentives for pediatric drug development.

Except for orphan drugs which are exempted from US PREA but not the EU Pediatric Regulation, the overall framework is quite similar across the two jurisdictions; both the US PREA and the EU Pediatric Regulation mandate submission of results from clinical studies that included the pediatric population specified in an agreed pediatric development plan (Pediatric Study Plan (PSP) in the US and Pediatric Investigation Plan (PIP) in the EU) before a marketing authorization (MA) application is considered valid unless requirements for pediatric

development have been waived or deferred until after MA. Thus, if appropriate measures are not taken to include the pediatric population during the drug development of novel drugs or already approved drugs still covered by a patent or a supplementary protection certificate, entry to the market can be blocked in the EU and the US.

Besides the exemption of orphan drugs in the US PREA, also the broader scope of the mandatory EU Pediatric Regulation compared to the US PREA has been highlighted as a major difference between the two legislations, and so have the broader options/reasons for granting a waiver by US FDA compared to EMA [20]. These differences can potentially lead to regional differences in the decisions on the requirements for the inclusion of the pediatric population during drug development. Such regional regulatory differences can have practical implications for applicants when running a global drug development program, which is critical to the conduct of effective, efficient, and ethical drug development for small populations, such as the pediatric population [20].

First, a difference in regulatory requirements can arise from the scope since the US PREA is restricted to the proposed indication(s) for the adult population, whereas the EU Pediatric Regulation provides a mandate for the European Medicines Agency (EMA) to require a drug development for the pediatric population for another indication *within* the condition of the proposed indication if a potential pediatric need exist [21]. Therefore, a PIP can cover an indication not intended by the applicant and therefore not granted at the initial MA, but only targeted in a PIP. In this way, potential pediatric use outside the proposed adult indication cannot be ignored. Second, a difference in regulatory requirements can arise from a difference in the grounds for granting waivers. The reasons for granting a waiver are more or less the same between the EU and the US, with one exception. In the US, a waiver can be granted based on the ground that the necessary studies are impossible or highly impracticable (e.g., because the patients are geographically dispersed), but this is not the case in the EU.

In 2007, a pediatric cluster was established between the EMA and the US Food and Drug Administration (FDA) with the objective of avoiding the exposure of children to unnecessary trials and facilitating global pediatric development plans based on scientific grounds, and compatible with both agencies' legislations [22]. However, consensus cannot always be reached based on different legislations, standards of care, and cultures [23]. It remains to be seen if this harmonization effort can facilitate regulatory understanding leading to similar regulatory decisions between the jurisdictions [24].

To our knowledge, only one study has benchmarked the requirements for pediatric drug development between the EU and the US. This study investigated the EMA decisions for waiver applications in the EU in relation to the US FDA, showing a high similarity in decisions [25]. However, the study did not give a complete overview of decisions in both regions, and it did not cover decisions for agreed pediatric development plans (PIPs or PSPs).

This study aims to provide a complete overview of the decisions by the EMA and the FDA to grant a waiver and/or to agree on a pediatric development plan (PIP or PSP) for indications granted at the initial time of MA for novel drugs approved in the EU and the US between 2010 and 2018. In addition, we analyze the concordance of regulatory decisions on the indications to be studied under a pediatric development plan for indications authorized in both regions. For this subset, we provide details on requirements for pediatric development plans for indications only subject to the EU Pediatric Regulation, but outside the scope of US PREA.

2.2 Technical considerations for excipient development in pediatric formulations

Excipients are subdivided into multiple functional classes dependant on their composition and the role they undertake in the final dosage form. The new excipients developed for paediatric formulations sometimes belong to more than one functional group (multifunctional) and hence, pose additional burden on the manufacturer to demonstrate their precise role during regulatory submissions.

There has been a considerable amount of mixed or co-processed excipients (not new chemical entities) introduced to the market for the development of fast disintegrating or dissolving dosage forms for children. Some examples of these are Ludiflash, Pharmaburst and F-Melt, which are usually a mixture of two or more excipients with contrasting functionalities to achieve desirable ready-to-use excipient blends. These products could simplify the formulation development process and reduce the associated technical challenges as the mixtures contain optimised amounts of diluent, disintegrant and binder. This in turn can provide the desirable target product profile of the orally disintegrating tablet (ODT) or the child-friendly dosage form.

Essentially, most of the ready-to-use excipients contain at least one polyol (sugar alcohol) such as mannitol or sorbitol alongside excipients which enhance swelling and disintegration of the tablet in few seconds. Other additional materials may include flavours or colourants to enhance the aesthetic properties of the dosage form.

Accordingly, some of these excipients require further characterisation of their composition to fully understand the functionality and physico-chemical / mechanical properties to support quality by design (QbD) to formulation development. It is also critical that analytical testing of co-processed excipients is performed to confirm no chemical change during processing.

Research groups have already started compiling information on excipient functionality in an electronic database. In our laboratory, functionality of excipients used in solid dosage forms for children were studied using novel methodologies that enhance our understanding of the composition of excipients on the nano and micro-scale. In addition, excipient-excipient and excipient-drug interactions were studied on the nano-scale to unveil scientific information on materials behaviour in the solid state to reduce the risk of interactions during downstream operations. Mannitol and MCC were some of the excipients investigated to elucidate the pros and cons of their use in children solid formulations.

In liquid oral formulation, the use of excipients including propylene glycol, benzyl alcohol, surfactants and ethanol is undesirable for children of certain ages due to inherent toxicities and incomplete maturation of metabolic function especially in neonates. Nevertheless, the substitute for these excipients is still largely missing and manufacturers are experiencing difficulties with finding appropriate paediatric excipients.

Despite that, research into novel excipients derived from natural chemical entities continued to overcome some of the solubility and palatability issues of medicines for children. There is a growing trend for the use of cyclodextrins as excipients for the delivery of poorly soluble drugs and for taste masking of paediatric oral liquid formulations. Cyclodextrins are ‘cup shaped’ molecules composed of cyclic oligosaccharides that were discovered in bacterial digest isolated from starch in 1891.

The cup shaped molecule inner cavity is hydrophobic while the outer surface is hydrophilic, hence poorly soluble or unpalatable drugs can be included inside the cup to prevent immiscibility or contact with the outside aqueous environment. In one study, midazolam, a preoperative anaesthetic commonly given to children, was successfully incorporated into γ-CD in order to mask its bitter acidic taste.

Parenteral products also contain excipients such as solubilisers, buffering agents, stabilisers and preservatives. These excipients present technical challenges such as the need for sterility besides the ability to withstand terminal sterilisation of aseptic processing. This in turn limits the choice of available excipients.

While the technical challenges in excipient research and development for paediatric formulations continue to appear especially with the future development of more complex entities from biotechnological sources, nevertheless, important questions have to be raised questioning the safety of these novel and multifunctional excipients – is there enough data to justify their use and will there be methods to predict their toxicological profile in paediatrics?

CONCLUSIONS

1. The innovation in excipients research has been struggling as a result of the gap in toxicity / safety data of materials in the pediatric population and because of the consequent regulatory obstacles. Regardless, some excipient manufacturers have shown willingness to fund toxicology studies for novel excipients to facilitate future drug development.

2. Given that new excipients use is only allowed as part of a new approved drug product, it is imperative that risk assessment is carried out on new excipients following the right regulatory procedure that ensures patient safety. Accordingly, efforts have been made both in America and Europe to establish an excipient safety database (STEP database) to facilitate excipients use in pediatric medicines.

CHAPTER III
THE CURRENT STATES AND FUTURE PERSPECTIVES OF PHARMACEUTICAL EXCIPIENTS IN PEDIATRIC PATIENTS IN DIFFERENT COUNTRY

Pediatric patients have different requirements compared to adults, regarding pharmacotherapy [26]. Flexible dosing, appropriate excipients, ease of administration, and dosage form acceptability or palatability are some of the key parameters for developing formulations appropriate for different age groups of the pediatric subset [27]. Pharmaceutical excipients are no longer considered inert in general, as new evidence suggests that there may be safety concerns with some excipients when used in products for the pediatric population, especially with younger age groups [28]. For example, immaturity of the metabolic and clearance functions, in neonates and infants, can lead to the toxicity of excipients such as propylene glycol [29], benzoic acid, and benzoates [30]. These excipients should, hence, be used with caution in noticeably young patients, such as preterm neonates. Paraben-containing drugs, injectable saline, and water for injections should be contraindicated in jaundiced newborn infants when the high-affinity albumin-binding sites approach saturation [31]. The use of benzalkonium chloride in the pediatric population has been reported to cause dose-related bronchoconstriction, especially in pediatrics who have asthmatic conditions, and has been related to the precipitation of respiratory arrest [32]. Ethanol, which is used as a solvent or a preservative agent in oral liquid preparations, has severe acute and chronic adverse effects in the pediatric population [33]. Flavoring agents may be used to impart taste, improve palatability, and thus, improve medication adherence. They are used in comparatively small amounts so that exposure is relatively low. However, there are safety concerns associated with flavoring substances, with respect to the potential risk of genotoxicity, allergy, and sensitization [34]. There are safety and biopharmaceutical challenges, of commonly-found excipients, in pediatric formulations [35].

Many excipients have no available safety data to justify their use during regulatory approval of the pediatric drug products. While the maximum oral safe dose for several kinds of excipients is known in the adult population [36], the acceptable excipient levels in pediatric patients (including preterm neonates) have not been established yet, due to the lack of evidence-based data [37]. Furthermore, the guidance or recommendation on excipient use for the pediatric population varies between countries around the world.

This thesis summarizes country-specific perspectives, including:

- the current state on the safety assessment of pharmaceutical excipients, in formulations for both adults and pediatrics (including the disclosure status of the excipients in the prescribed drugs) and challenges in excipient regulation;
- ongoing efforts for ensuring the safety of excipients, for the pediatric population, through the pediatric drug development in Europe and the United State of America (US). Additionally, country-specific perspectives were compared, and aspects of past and ongoing collaborative efforts on excipients used for the pediatric population are presented (Figure 3.1).

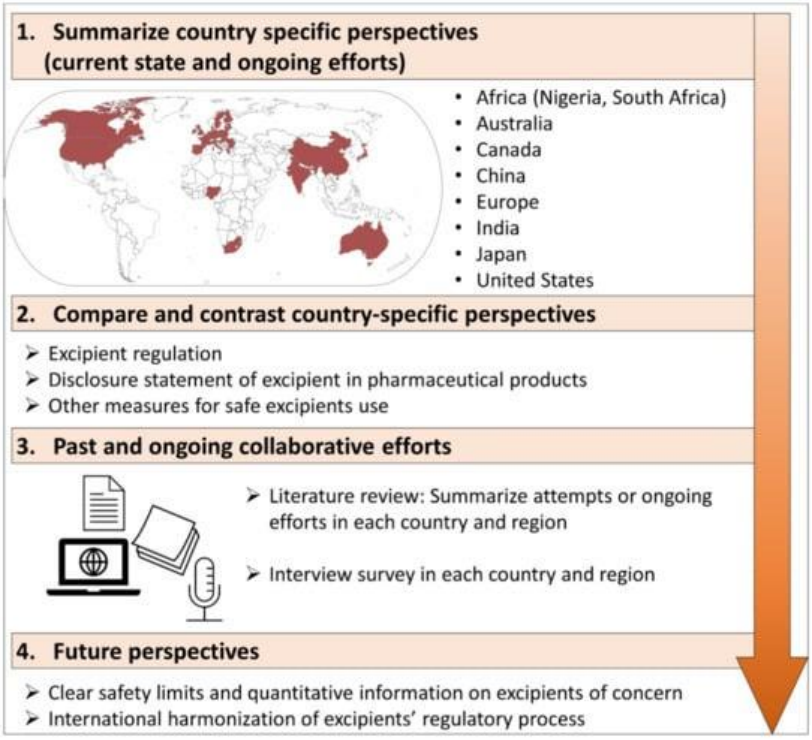

Figure 3.1. Concept and summary of this study.

3.1. Country-Specific Perspectives

A guideline on ‘Excipients in the labeling and package leaflet of medicinal products for human use’ released by the EC. Excipients with a known action or effect are listed in the amended guideline. and, therefore, must appear on the labeling of all medicines in the EU [38]. The Annex also contains the safety information for the specified excipients that must be included in the medicine’s package leaflet. The EMA’s website has background information on the safety of individual excipients. [39].

Regarding the disclosure of quantitative information on pharmaceutical excipients, Article 59(1)(f)(iv) requires the full qualitative composition (inactive substances and excipients) and the quantitative composition of active substances to be included in the package leaflet [40]. All excipient names on the labeling, package leaflet, and Summary of Product Characteristics (SmPC) must comply with the following. Individual excipients should not have proprietary names. Fragrance and flavor ingredients can be declared in general terms (e.g., ‘orange flavor’, ‘citrus perfume’); it is necessary to declare a recognized action or effect. For excipients that are categorized in a chemical group in the Annex but are not explicitly listed (e.g., other salts), the information applies unless justified. pH adjusters should be mentioned by name, and their function may also be indicated in the package insert, e.g., hydrochloric acid and sodium hydroxide for pH adjustment. For some of the excipients in the Annex, the information may be included in the warnings section of the package insert (i.e., pregnancy and lactation, pediatric use, undesirable effects, warnings and precautions, contra-indications). Additionally, it may be necessary to refer to the excipient warnings section from other sections in the package leaflet. In the case of ethanol, it will be necessary to refer to the excipient warnings section from those sections relating to effects on the ability to drive, pregnancy and lactation, information for children, etc.

A ‘threshold’ value is also included in the Annex. However, the stated information is not a safety limit. Thresholds are expressed as the quantity of an excipient at the maximum daily dose (MDD) of the medicinal product, as indicated

in the SmPC. When the text refers to the term ‘per dose’ it means the dose of the medicinal product.

Regarding the toxicology study in juvenile animals, the aspects are the same as US regulations. When the use of an excipient, in drugs for the pediatric population, cannot be justified based on existing information sources, toxicology studies for an excipient in juvenile animals may be necessary [41].

Regarding information on the safety of excipients, the EMA proposed safety limits for several excipients in the pediatric population, such as propylene glycol [42] and sorbitol [43]. In January 2014, the EMA proposed the inclusion of more detailed information on alcohol content in PILs, as well as alcohol content thresholds for different age groups, in a draft for the guideline on ‘Excipients in the label and package leaflet of medicinal products for human use’ [44]. Acceptable daily intake for artificial sweeteners, such as aspartame and saccharin, is also stated in the National Health Service United Kingdom (UK) [45]. However, this information is not specified for pharmaceutical excipients. Regarding the novel excipients, such as hydroxypropyl-β-cyclodextrin, there is insufficient safety data on pediatric patients, especially on neonates [46].

As an available database, the STEP database is a user-designed free resource that compiles the safety and toxicity information of excipients, which is manually extracted from selected information sources [47]. Currently, the database includes 75 excipients, most of which are used in oral dosage forms. O’Brien et al. conducted a pilot review, identifying excipients in parenteral products, used for pediatrics in India, from the STEP database [48], and found that, of the 30 identified excipients for 104 parental products that are commonly used in pediatric population in India, only 10 excipients were included in the STEP database. This study will also be extended to other countries, such as UK and Ireland, to identify the excipients used in parenteral products and prepare a comprehensive list of excipients used in parenteral products, as well as those to be included in the STEP database. Further efforts are required by the sponsors to share and declare non-confidential in-house

data, on the STEP database, to be a useful database and prevent repeated studies on excipient safety.

Excipient guidelines from the FDA is mostly based on IPEC recommendations. To ensuring the safety, guidelines addressed the safety tests generally required to determine the safety of a new excipient [49]. However, unlike drugs, testing for a new excipient should be evaluated on a case-by-case basis. The USP published the IPEC Safety Guidelines as the General Chapter on Excipient Biological Safety Evaluation Guidelines. The FDA guidance refers to the ICH Safety Testing Guidelines for conducting testing for new excipients. In the US, DMF systems exist for excipients to support medication applications. The IPEC-Americas Master File Guide is a format guide for DMF submissions that may be used to create uniform excipient information. [50]. Excipients, colorants, taste, essence, or material employed in their manufacturing are all classified as Type IV DMFs in the US. In support of a new drug application, DMFs can be utilized to give information to the FDA. [51]. Testing strategies for short-, intermediate-, and long-term usage are also discussed in the FDA regulation. The use of a "family approach" to assess the safety of related excipients, such as various viscosity or molecular weight grades of a polymer excipient, has recently been discussed between industry and the FDA. This technique is presently being discussed, and it is intended to allow some flexibility in the use of safety information that includes a variety of related excipients to support the safety of a specific class in the family when safety information unique to that class is not available. However, it is not clear whether this approach can apply to pharmaceutical products for the pediatric population.

To obtain approval for pediatric products, juvenile toxicity studies must be conducted in representative animal species to demonstrate the safety of the drug and the excipients used in the drug. There is no separate approval process for excipients in pediatric products. Color additives and flavors, unlike other excipients, are regulated separately from therapeutic uses. These substances are evaluated for safety in processes outside of the drug review process. All color additives in the US are subject to premarket approval by the FDA. Color additives listed in 21 CFR, Parts

74 and 82, must be analyzed and batch-certified by the FDA. In the case of a new flavoring substance, such substances can be evaluated by the Flavor and Extract Manufacturers Association (FEMA) of the US Expert Panel to determine if they are Generally Recognized as Safe (GRAS). Flavoring agents are determined to be GRAS by the FEMA Expert Panel under the authority granted in Section 201(s) of the FD&C Act. To support the safe use of a particular flavor, references to the FEMA GRAS evaluations can be included in the product application. The restricted availability of and access to safety data, as well as uncertainty in extrapolating exposure and effects between adults and children or nonclinical animals and humans, complicate the safety qualification of excipients for pediatric usage. Although regulatory guidance provides some guidance on the safety assessment of excipients [51], there is a lack of uniformity on what is acceptable or essential to effectively assess the risk-benefit profile of an adjuvant in various pediatric demographics and disease states. When the use of an excipient in a pediatric medical product cannot be justified based on available information sources, toxicology studies in juvenile animals may be required. [52]; however, the standardized conduct of juvenile toxicology studies in a routine "box-ticking" manner is not considered appropriate. If the effects on growth and development have not been previously documented, the safety evaluation should focus on them. [53]. The juvenile toxicity study can be designed to assess the safety of both the excipient and the active substance [54]. Details of nonclinical juvenile toxicity studies, as well as any clinical safety evaluation undertaken by a pharmaceutical industry to certify excipients as part of a medicinal product, are not disclosed to the public.

The USP 35/National Formulary 30 lists over 40 different functional categories for excipients [55]. USP General Notices 5.20 and 5.60 require excipients (additives and processing aids) to be on labels and reported when used at levels >0.1% (based on the International Council for Harmonization Q3B). While IPEC-Americas considers that excipient and pharmaceutical companies should communicate openly regarding the potential for the presence of additives 56[], this can include the use of confidentiality disclosure agreements during excipient/supplier qualification.

The quantities of the excipients included in the final product are not listed in the labeling of each product. Several excipients, such as alcohol and solubilizer, which may cause hypersensitivity or other adverse reactions, shall be included in the label along with the amount. If a drug includes one or more inactive substances that are linked to a major safety concern in pediatric patients (all pediatric patients, particular pediatric age groups, or subgroups), the risk must be disclosed on the label [57]. In general, a substantial safety risk associated with an inactive component should be detailed in the boxed warning, contraindications, and/or warnings and precautions section, as well as stated in the pediatric usage part.

The screening and careful selection of excipients in a pediatric medicinal product is, thus, challenging due to lack of appropriate guidance on safety qualification and risk assessment of excipients for pediatric formulations.

The Inactive Ingredient Database (IID) is an open information database for pharmaceutical excipients that offers information on inactive substances (excipients) found in FDA-approved prescription formulations. This data can be utilized by the pharmaceutical industry to help create new drugs. Once an inactive component appears in an authorized drug product for a certain route of administration, it is no longer considered novel for new drug development reasons and may require a less thorough assessment. For example, if a certain inactive component has been authorized in a specific dosage form and potency, a sponsor could consider it safe for use in a similar way in a similar product. In this database, the maximum potency of each excipient per unit dose is available, including enteral formulation. If a new drug application intends to use an inactive ingredient at a level that exceeds any of the IID listings without reason, the FDA will reject it. An inactive ingredient is considered justified, for receipt purposes, if the proposed level is at or below the amount indicated in the IID for the corresponding route of administration of the drug product. The IID, on the other hand, does not yet give information on the various exposure models (e.g., Maximum Daily Intake (MDI) based on the labeled dosage guidelines)., safety in pediatric populations, and acute versus chronic use) that may be needed during such a technical review. Some values are difficult to verify in some

circumstances since they are related with old products. In other cases, the use of the term “NA” in place of a maximum potency may be used when the quantity of the excipient is variable (e.g., pH adjusters that are indicated in the formula as “quantity sufficient”). The FDA has updated the IID database, allowing users to run electronic queries to acquire correct MDI and MDE information for any route of administration for which data is available. MDE is the total amount of the excipient that would be taken or used in a day, based on the MDD of the drug product in which it is used. MDE is calculated as the dosage unit level of the excipient multiplied by the maximum number of dosage units recommended per day. MDE may also be referred to as MDI for oral drug products. When determining excipient MDE, the FDA will evaluate the applicant’s rationale for an MDD if it is not included in the product labeling.

IID does not differentiate between adult and pediatric products currently. The maximum allowable dose of excipient listed in IID may not be safe for pediatric use if the excipients have potential for causing any harmful effects due to patient age, so additional studies or precedence of use, in the same age group with similar use duration, may be needed to justify use of such excipients in pediatric products.

A risk-benefit approach should be used in safety assessments, as opposed to an approach where the safety assessment is only in the context of potential risks. This is particularly important, as most pharmaceutical products could not be manufactured without the use of excipients. In situations where the benefit-risk cannot be adequately characterized on the basis of prior use in pediatric patients, use of the excipient cannot be bypassed, but the therapeutic benefit of the drug is sufficient, it may be useful to proceed carefully and assess safety in the clinical setting.

Efforts are needed from both pharmaceutical and excipient manufacturers to fill in the gaps and identify the best practices and types of data needed for the safety assessment of novel excipients. For instance, the Novel Excipients Working Group (members from IPEC-Americas and the IQ Consortium) and a similar group, formed within IPEC-Americas, are currently exploring the development of common best

practices for nonclinical safety (testing and specification requirements) and creating a process to draft a well-defined, nonclinical data package for novel excipients [60]. USP also supports a novel excipient review program, which contributes to establishing new pathways for the development, and facilitating innovation for the advancement of, new medical products [59].

3.2 Common and difference requirements

Excipient regulation, disclosure statements of excipient in pharmaceutical products, and other measures for safe excipient use in each country and region (table 3.1). The regulatory processes for excipients included in the pharmaceutical product are similar between jurisdictions; however, information gaps remain. There are some resources for the judgment of excipient use in pediatric formulation through the regulatory process in the US or EU. However, there is no available database elsewhere. EMA and FDA proactively published several guides about acceptable daily intake of some excipients; however, no guidance or guidelines exists in other regions. The law and process for pediatric drug development may make a difference among the countries and regions.

Table 3.1

Excipient regulation, disclosure statements of excipient in pharmaceutical products, and other measures for safe excipient use in each region

Country/Region	Regulation on Pharmaceutical Excipients	Disclosure of Excipients Information	Quantitative Information	Any other Special Measures for Safety of Excipients Use for Pediatrics
EU	• Reviewed by EMA following the EC guidelines	• The full qualitative composition • The list of excipients which must feature on the labelling of medicinal products and the way in which these excipients must be indicated • Some concerned excipients are described in the excipient warnings section from other sections in the package leaflet. • 'Threshold' values are indicated in the guidelines	• Not for all excipients.	• STEP database
US	• Reviewed by FDA following the FDA guidance or a novel excipient review program	• Excipients that may cause hypersensitivity or other adverse reactions need to be included along with the amount	• Not required for all excipients.	• FDA IID

Country/Region	Regulation on Pharmaceutical Excipients	Disclosure of Excipients Information	Quantitative Information	Any other Special Measures for Safety of Excipients Use for Pediatrics
	• Flavoring agents are evaluated by FEMA independently	• Excipients with a significant safety concern in pediatric patients must be described in package insert		

The disclosure status of information on pharmaceutical excipients was similar among countries; that is, not all quantitative data was disclosed, and some excipients, such as pH adjusters and flavoring agents, were not specified in the product information. Some coloring agents and sweeteners that are not approved in one country were used in other countries. The function of sugar in formulation and amount of alcohol used are recommended to be stated in the package insert in the European countries and South-Africa, but there is no regulation for it in the other regions. As with any other special measures for the safety of the use of excipients for pediatric patients, the US and EU are attempting to create a database that contributes to the safety assessment of the use of excipients in the pediatric population.

Regarding the 'threshold', MDI, or contraindication of the use of excipients in the pediatric population, most countries declined to specify because the evidence-based quantitative information on the use of excipients in the pediatric population is insufficient.

Summary of attempts or ongoing efforts in each country and region was indicated in table 3.2.

Table 3.2.

Summary of attempts or ongoing efforts in each region

Country/Region	Other Attempts or Ongoing Efforts
EU	Study on excipient exposure in pediatrics, ESNEE project, SEEN project, Workshop for the Safety Qualification of Excipients
US	Study on excipients exposure in pediatrics Incude pediatric safety in FDA IID Nove excipient review pilot program by CDER Workshops, survey, and pediatric excipient risk assessment framework development by IQ pediatric consortium

3.3 Safety Qualification of Excipients. The sessions were held on the 8th and 9th of June 2016 at a public workshop titled “Challenges and Strategies to Facilitate Formulation Development of Pediatric Drug Products.” [61]. The existing state and gaps, as well as ideas for risk-based techniques to facilitate the development of pediatric age-appropriate pharmacological products, were discussed during this session. The goal of the session was to bring together a diverse group of stakeholders (e.g., EU and US-based formulators, regulators, clinicians, and toxicologists) to discuss approaches to excipient safety assessment and to identify gaps and challenges in current paradigms for assessing excipient safety and evaluating potential risk in pediatric formulations. The necessity of a systematic, risk-based, proportional approach to safety evaluations was underlined by the participants throughout this event. The proposed risk-based strategy should only be utilized when an excipient is expected to be critical to the formulation’s performance. The interpretation of all the data might lead to recommended measures for excipients with a high toxicity potential for children, more research to better understand the potential dangers, or clinical monitoring of exposure or biomarkers of safety. Using orthogonal data sources, collaborative data sharing, and better awareness of existing sources, such as the STEP database and IID, were all considered significant in this session to close the gap in excipient information needed for risk assessment. The workshop’s organizers and attendees emphasized the need of establishing risk-based approaches for excipient safety evaluations, as well as the importance of meaningful stakeholder (e.g., patient, caregiver) involvement in pediatric formulation development.

The Safe Excipient Exposure in Neonates and Small Children (SEEN) project was a retrospective cohort study. Based on a chart audit of multi-medicated patients under the age of 5, the SEEN project quantifies the total amount of excipients administered to poly-medicated neonatal and pediatric patients during hospitalization, and investigate whether any medical diseases are treated in European countries with potentially harmful excipients. As part of this project, the cumulative daily alcohol exposure (mg/kg/day) in polymedicated neonates and

infants was measured. [62]. The findings revealed a lack of understanding of the acceptability of various dose forms, tastes, and, more crucially, the safety of formulation excipients in relation to children's age and developmental stage.

At the end of 2009, a group of neonatal and pharmaceutical professionals from around Europe (Liverpool, Leicester, Belfast (UK); Paris (France); Tartu (Estonia)) gathered to discuss the present state and challenges of newborn excipient exposure. [63]. Their major goal was to give evidence for discussion about excipient. The consortium was formed, and the European Study of Neonatal Exposure to Excipients (ESNEE) was launched, by supporting from "Priority Medicines for Children (PRIMEDCHILD)". ESNEE is a research project aimed at developing a set of procedures that will allow for an integrated assessment of neonatal exposure to potentially hazardous excipients in pharmaceutical products in Europe. The project creates new methodologies and gives knowledge that is needed for formula development and application. The ESNEE program comprises the following six work packages:

- to undertake a comprehensive, European-based questionnaire and a point prevalence survey, of excipient exposure in neonates, to highlight opportunities for product substitution and priorities for reformulation;
- to conduct a systematic review to identify existing information about the impact of excipients on the development of human neonates and juveniles in other species;
- to develop techniques that allow small-volume blood samples to be used in population excipient kinetic (EK) models for systemic excipient exposure in human neonates;
- to conduct a cohort study of neonates exposed to selected excipients, including blood samples for EK assays;
- to develop EK models for selected excipients;

to integrate the results of the objectives, in work packages one to five, to detect formulation problems associated with the use of excipients in neonates Through this

ESNEE program, Nellis et al. surveyed excipient uses in Europe in 2015 but found that manufacturers were reluctant to share the quantitative information for many products [61]. Additionally, Mulla et al. conducted a kinetic study for an excipient in the target population, for methyl and propyl parabens, in the same year [62].

Selecting excipients with appropriate safety and tolerability is a major hurdle in pediatric formulation development. The suitability of a particular excipient will be dependent on the context of its users, such as the pediatric age range, acute versus chronic use, clinical risk/benefit of the disease, activity level, and excipient type. Scientists are encouraged to apply the principle of risk/benefit balance to assess the suitability of excipients to the specific pediatric population. An indicative list of parameters that should be taken into consideration and a hierarchy of information sources, when assessing the excipients' risks, are provided by regulatory agencies. However, the approach to be taken and details of how the risk evaluation should be undertaken are lacking. Recently, a systematic approach called the "Paediatric Excipient Risk Assessment (PERA) framework", to guide the selection of excipients and assessment of the risk of excipient exposure, has been developed through collaboration between IQ Consortium and EuPFI pediatric excipient sub-groups, which will be published soon [63]. The application of the PERA framework is key to both efficient product development and regulatory decision making. Proper application of PERA framework can lead to better communication and optimal discussions between excipient manufacturers, pharmaceutical product manufacturers, and regulatory agencies.

The harmonization of standards among the pharmacopeia is one way to reduce this burden. In 1989, the Pharmacopeial Discussion Group (PDG) was formed, with representatives from the organizations that developed the JP, Ph. Eur., and USP–NF, to work toward the harmonization of pharmacopeial standards, such as excipient monographs [64]. Harmonization status can be referred to on the website of the Council of Europe. The published table summarizes the sign-off coversheets for all

monographs of excipients under the PDG work plan. These coversheets provide detailed, helpful information about harmonized parts and local requirements for all individual texts, having undergone harmonization by the PDG.

Several authorities attempt to refer to the guidelines or guidance published in the other countries or regions for the safety assessment of excipients. Harmonizing the ICH guidelines and the use of the open-source database may accelerate the excipient regulation process. Not all countries and regions introduce this system, and further improvement is needed.

Regarding the ICH guidelines, the ICH S11 recommends an approach for the nonclinical safety evaluation of pharmaceutical excipients intended for development in pediatric populations [65]. To assess the safety of the excipients in a pediatric clinical formulation, available information on the excipients should be evaluated, and a weight of evidence approach (an assessment based on the entirety of the evidence, including the pharmacology, pharmacokinetic (ADME), nonclinical in vitro and in vivo animal studies, and the safety data from clinical settings) should be followed. If sufficient data to support the use of the excipient in the intended pediatric population is not available, further safety evaluation can be required. e.g., evaluating the excipient alone in a juvenile animal toxicity study. Since these guidelines only focus on nonclinical evaluations of pharmaceuticals including excipients' safety for pediatrics, implementing the ICH guidelines may not always ensure excipients' safety in clinical settings.

A real-world excipient exposure in preterm infants and neonates has previously been assessed, for several substances in various regions, by referencing product information [66]. However, limited information makes it impossible to evaluate the actual risk of excipients to the pediatric population.

Attempts of quantitative evaluations of excipient exposure, by using the donated blood samples, have also been tried [67] to evaluate an accurate and actual influence of excipients on pediatric patients, including neonates.

In this review, we compared country-specific perspectives, including the current state on the safety assessment of pharmaceutical excipients, in formulations for both adults and pediatrics (including the disclosure status of excipients in pharmaceutical products,) and challenges in excipient regulation. Additionally, ongoing efforts for ensuring the safety of excipients for the pediatric population were summarized, and further possibilities of collaboration worldwide were discussed.

Manufacturers' SmPC's, package inserts, and PILs may be useful for identifying the excipients in particular medicine, and they may help determine the specific amounts of excipients present in pediatric formulations. However, there are many excipients in approved medicines that contain undeclared additives and concomitant components because excipient manufacturers have not been willing to disclose the identity of such components, due to the proprietary nature of their use, and there is no obligation of indication. Not all quantitative data is available in all countries or regions, and proper risk assessment has not been utilized for safety assessments for pediatric patients. Although some excipients were disclosed with quantitative information, and the extents of exposure were evaluated through dedicated investigations, the criteria and evaluation results were ambiguous. Furthermore, because most prescriptions for neonates, including preterm neonates, are "off-label" [68], there was no stringent regulation for manufacturers to identify the safety of the excipients in this pediatric population. As shown in the previous review report, toxicities and adverse effects of major used pharmaceutical excipients, on pediatric patients, were summarized [69]. Safety assessment is difficult and complicated. Safety concerns on the use of excipients are dependent on each patient's background, such as age, including postmenstrual weeks and underlying disease (i.e., sweeteners have a risk for diabetes [70], saccharin is recommended to use only for children greater than 3 years [71]). Furthermore, the severity of toxicity caused by the excipients' exposure is different. A risk assessment should be done, through the drug development and regulatory process, before use in

clinical settings. Juvenile toxicity study can also be required, extensively, to assess the toxicities or sensitivities of excipients to pediatrics, even when the drugs used for pediatrics are expected [72]. The current status of challenges on excipient safety for pediatrics, and its solution, was summarized in table 3.3.

Table 3.3

Safety issues on pharmaceutical excipients for pediatric patients

Challenges	Lack of evidence-based safety data considering physiological, toxicokinetic, and toxicodynamic changes in pediatrics
	Lack of evidence-based safety data for the special population (i.e., preterm neonates, patients with specific disease)
	A safety evaluation of excipients in not only a pediatric formulation but also off-label used products is necessary before use referring to accessible safety data
	Because accessible data are from adult human and animals, safety data from pediatric use and juvenile toxicity studies will be required.
Solution	The evidence-based safety information of excipients should be included into the repository database as an accessible information on stakeholders

In the regulatory process, the excipients included in the pharmaceutical products are reviewed by regulatory authorities in each country or region. However, background information on excipient safety for the pediatric population is lacking. As shown in the attempts of the EU, guidelines on excipient use and its labeling in the package leaflet of medicinal products will be needed for each region. More preferably, preparing the common and harmonized guidelines, or guidance, for excipient use and its labeling in the package leaflet will be desired. As shown in the recent review, various criteria were set based on the several guidelines for each excipient. The pharmacopoeias among EU and the US, which are the base of the

excipients' monograph in each country, have not been harmonized. The evidence base and determination process for the recommended doses is also different. Common harmonized guidelines and a unified excipients database may be helpful for regulatory authorities and healthcare professionals that are dedicated to pediatric patients. In addition to the safety profile, a list of excipients that can or cannot be used for pediatric pharmaceutical products will be helpful. The stakeholders in many countries are confronting common problems. Sharing those issues and hammering out effective measures would be beneficial. Looking into the current situation all over the world, through this review, may help the stakeholders overcome the current situation.

3.4. Future Perspectives of Pharmaceutical Excipients in Pediatrics Drugs

To resolve this situation, a survey based on real-world prescription data and a quantitative risk assessment, by academia and clinical healthcare professionals, will be needed. As described in this review, information availability varies among countries in the world, and quantitative information on excipients, and their safety for pediatric patients, are rarely specified. As shown in several open databases (i.e., STEP database, IID), the enhancement of accessibility for data on excipients was found; however, evidence-based quantitative data for tolerated daily intake of each excipient for the pediatric population is still lacking. Clearer safety limits and quantitative information, for the problematic excipients in the pediatric population, are needed to aid healthcare professionals in drug selection for these patients. This is especially important in neonates and young children, as well as when patients are taking multiple, and long-term, medications, when considering the potential cumulative adverse effects.

For the evidence-based excipient regulation, collecting the evidence-based data for the safety of excipients in the pediatric population, gathering information on currently used excipients in pharmaceutical products, including quantitative

information, and sharing the current issues of excipient exposure in pediatric patients with all stakeholders, including regulatory authorities in every country or region, is imperative. Additionally, a harmonized guideline with clearer safety limits and quantitative information, on excipients of concern, in the pediatric population for each country or region, will be needed. Internationally harmonized excipients' regulatory processes may contribute to ensuring safe medicinal treatment for the pediatric population.

CONCLUSIONS

It has been determined that for evidence-based regulation of the use of excipients, the collection of evidence-based data on the safety of excipients in the pediatric population, the collection of information on excipients currently used in pharmaceutical products, including quantitative information, and sharing current issues of excipient exposure in pediatric patients with all stakeholders, including regulatory authorities in each country or region, is imperative.

It was determined that a harmonized guideline with clearer safety limits and quantitative information on excipients of concern for the pediatric population for each country or region would be needed.

It has been established that internationally harmonized processes for the regulation of excipients can contribute to the provision of safe drug treatment for children.

GENERAL CONCLUSIONS

Pediatric drug products require specialized consideration in formulation development. Recent changes to US and European regulatory requirements for

pediatric drugs have transformed what once was only a niche area to an important field in drug development.

It has been established that there is an urgent need for pharmaceutical products tested and approved as safe and effective for use by children. From 1973–1997, the percentage of approved drugs that did not contain any pediatric labeling information remained fairly stable at 71–81%. Of the 33 new molecular structures approved in 1997, 27 had potential for pediatric use, but only nine contained any pediatric labeling information (2). Two-thirds of drugs currently prescribed to children have not been studied or labeled for pediatric use.

The innovation in excipients research has been struggling as a result of the gap in toxicity / safety data of materials in the pediatric population and because of the consequent regulatory obstacles. Regardless, some excipient manufacturers have shown willingness to fund toxicology studies for novel excipients to facilitate future drug development.

Given that new excipients use is only allowed as part of a new approved drug product, it is imperative that risk assessment is carried out on new excipients following the right regulatory procedure that ensures patient safety. Accordingly, efforts have been made both in America and Europe to establish an excipient safety database (STEP database) to facilitate excipients use in pediatric medicines.

It has been determined that for evidence-based regulation of the use of excipients, the collection of evidence-based data on the safety of excipients in the pediatric population, the collection of information on excipients currently used in pharmaceutical products, including quantitative information, and sharing current issues of excipient exposure in pediatric patients with all stakeholders, including regulatory authorities in each country or region, is imperative.

It was determined that a harmonized guideline with clearer safety limits and quantitative information on excipients of concern for the pediatric population for each country or region would be needed.

It has been established that internationally harmonized processes for the regulation of excipients can contribute to the provision of safe drug treatment for children.

REFERENCES

1. Osterberg RE, Demerlis CC, Hobson DW, McGovern TJ. Trends in Excipient Safety Evaluation. International Journal of Toxicology 30, 600-610 (2011)
2. United States Pharmacopeial Convention. USP and NF Excipients, Listed by Category. USP 35-NF 30 USP, Rockville, MD, USA, 2011, p. 4
3. Brniak W, Jachowicz R, Krupa A, Skorka T, Niwinski K. Evaluation of Co-processed Excipients Used for Direct Compression of Orally Disintegrating Tablets (ODT) Using Novel Disintegration Apparatus. Pharmaceutical Development and Technology 18, 464-474 (2013)
4. Al-Khattawi A., Mohammed AR. Compressed Orally Disintegrating Tablets: Excipients Evolution and Formulation Strategies. Expert Opinion on Drug Delivery 10, 651-663 (2013)
5. International Pharmaceutical Excipients Council. The IPEC Excipient Composition Guide (2020)
6. Wang T. The Creation of an Excipient Properties Database to Support Quality by Design (QbD) Formulation Development. American Pharmaceutical Review
7. http://www.americanpharmaceuticalreview.com/Featured-Articles/140508-The-Creation-of-an-Excipient-Properties-Database-to-Support-Quality-by-Design-QbD-Formulation-Development/> Accessed online (20/Dec/2013)
8. Allegaert K. Propylene Glycol in Neonates: Never Prescribed, Frequently Administered, Hardly Evaluated. Journal of Clinical Toxicology 2 (2012) doi: http://dx.doi.org/10.4172/2161-0495.1000e113
9. Van den Anker, J.; Reed, M.D.; Allegaert, K.; Kearns, G.L. Developmental Changes in Pharmacokinetics and Pharmacodynamics. *J. Clin. Pharmacol.* 2018, *58*, S10–S25.
10. Walsh, J.; Ranmal, S.R.; Ernest, T.B.; Liu, F. Patient acceptability, safety and access: A balancing act for selecting age-appropriate oral dosage forms for paediatric and geriatric populations. *Int. J. Pharm.* 2018, *536*, 547–562.
11. European Medicines Agency (EMA). *Guideline on Pharmaceutical Development of Medicines for Paediatric Use*; EMA: London, UK, 2013; Available

online: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf (accessed on 2 February 2022).

12. Allegaert, K. Propylene Glycol in Neonates: Never Prescribed, Frequently Administered, Hardly Evaluated. *J. Clin. Toxicol.* 2012, *2*, 9.
13. European Medicines Agency (EMA). *Questions and Answers on Propylene Glycol Used as an Excipient in Medicinal Products for Human Use*; EMA: London, UK, 2017; Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-propylene-glycol-used-excipient-medicinal-products-human-use_en.pdf (accessed on 2 February 2022).
14. European Medicines Agency (EMA). *Questions and Answers on Benzoic Acid and Benzoates Used as Excipients in Medicinal Products for Human Use*; EMA: London, UK, 2014; Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-benzoic-acid-benzoates-used-excipients-medicinal-products-human-use_en.pdf (accessed on 2 February 2022).
15. Andersen, A. Final amended report on the safety assessment of methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzylparaben as used in cosmetic products. *Int. J. Toxicol.* 2014, *27*, 1–82.
16. Lee, B.H.; Kim, S.H. Benzalkonium chloride induced bronchoconstriction in patients with stable bronchial asthma. *Korean J. Intern. Med.* 2017, *22*, 244–248.
17. Zuccotti, G.V.; Fabiano, V. Safety issues with ethanol as an excipient in drugs intended for pediatric use. *Expert Opin. Drug Saf.* 2011, *10*, 499–502.
18. Walsh, J.; Cram, A.; Woertz, K.; Breitkreutz, J.; Winzenburg, G.; Turner, R.; Tuleu, C. Playing hide and seek with poorly tasting paediatric medicines: Do not forget the excipients. *Adv. Drug Deliv. Rev.* 2014, *73*, 14–33.
19. Rouaz, K.; Chiclana-Rodríguez, B.; Nardi-Ricart, A.; Suñé-Pou, M.; Mercadé-Frutos, D.; Suñé-Negre, J.M.; Pérez-Lozano, P.; García-Montoya, E. Excipients in the Paediatric Population: A Review. *Pharmaceutics* 2021, *13*, 387.

20. Belayneh, A.; Tadese, E.; Molla, F. Safety and biopharmaceutical challenges of excipients in off-label pediatric formulations. *Int. J. Gen. Med.* 2020, *13*, 1051–1066.
21. British Medical Association and Royal Pharmaceutical Society of Great Britain. General Guidance: Excipients. In *Joint Formulary Committee*; British National Formulary 2013–2014 Edition; British Medical Association and Royal Pharmaceutical Society of Great Britain: London, UK, 2014.
22. National Agency for Food and Drug Administration and Control (NAFDAC). *Quality Guidelines for the Registration of Pharmaceutical Products for Human Use in Nigeria*; NAFDAC: Abuja, Nigeria, 2020. Available online: http://www.nafdac.gov.ng/wp-content/uploads/Files/Resources/Guidelines/R_and_R_Guidelines/GENERAL/Quality-Guidelines-for-Registration-of-Pharmaceutical-Products26381.pdf (accessed on 2 February 2022).
23. National Agency for Food and Drug Administration and Control (NAFDAC). *Label Guidance*; NAFDAC: Abuja, Nigeria, 2021. Available online: https://www.nafdac.gov.ng/wp-content/uploads/Files/Resources/Guidelines/R_and_R_Guidelines/More_On_R_and_R/Guidelines-for-Labelling-26375.pdf (accessed on 2 February 2022).
24. National Agency for Food and Drug Administration and Control (NAFDAC). *Good Clinical Practice Guidelines 2020*; NAFDAC: Abuja, Nigeria, 2020. Available online: https://www.nafdac.gov.ng/wp-content/uploads/Files/Resources/Guidelines/CTD_Guidelines/NAFDAC-Good-Clinical-Practices-Guidelines-2020.pdf (accessed on 2 February 2022).
25. National Agency for Food and Drug Administration and Control (NAFDAC). *Guidelines for Clinical Trial in Paediatric Populations*; NAFDAC: Abuja, Nigeria, 2021. Available online: https://www.nafdac.gov.ng/wp-content/uploads/Files/Resources/Guidelines/DRUG_GUIDELINES/GUIDELINES-FOR-CLINICAL-TRIAL-IN-PAEDIATRIC-POPULATIONS-1.pdf (accessed on 2 February 2022).

26. National Agency for Food and Drug Administration and Control (NAFDAC). *Non-Nutritive Sweeteners Prohibition in Drugs Regulations 2019*; NAFDAC: Abuja, Nigeria, 2019. Available online: https://www.nafdac.gov.ng/wp-content/uploads/Files/Resources/Regulations/DRUG_REGULATIONS/Non-nutritive-sweeteners-Prohibition-in-Drugs-Regulations-2019.pdf (accessed on 2 February 2022).
27. Akinyandenu, O. Counterfeit drug in Nigeria: A threat to public health. *Afr. J. Pharm. Pharmacol.* 2013, *7*, 2571–2576.
28. Soremekun, R.; Ogbuefi, I.; Aderemi-Williams, R. Prevalence of ethanol and other potentially harmful excipients in pediatric oral medicines: Survey of community pharmacies in a Nigerian City. *BMC Res. Notes* 2019, *12*, 460.
29. South African Health Products Regulatory Authority (SAHPRA). *Guideline for Professional Information for Human Medicine (Categories A and D)*; SAHPRA: Pretoria, South Africa, 2020. Available online: https://www.sahpra.org.za/wp-content/uploads/2020/02/2.16_Guideline-for-Professional-Information-for-Human-Medicines-Categories-A-and-D_Jul19_v2-1.pdf (accessed on 2 February 2022).
30. South African Health Products Regulatory Authority (SAHPRA). *Reliance Guideline*; SAHPRA: Pretoria, South Africa, 2020. Available online: https://www.sahpra.org.za/wp-content/uploads/2021/11/Reliance-Guideline_v2_23-Oct-2021.pdf (accessed on 2 February 2022).
31. South African Health Products Regulatory Authority (SAHPRA). *Guideline for Patient Information Leaflet for Human Medicines (Categories A and D)*; SAHPRA: Pretoria, South Africa, 2020. Available online: https://www.sahpra.org.za/wp-content/uploads/2020/02/2.14_Guideline-for-Patient-Information-Leaflet-for-Human-Medicines-Categories-A-and-D_Jul19_v2-1.pdf (accessed on 2 February 2022).
32. South African Health Products Regulatory Authority (SAHPRA). *Quality and Bioequivalence Guideline*; SAHPRA: Pretoria, South Africa, 2020. Available online: https://www.sahpra.org.za/wp-content/uploads/2020/02/2.02_Quality-and-Bioequivalence-Guideline_Jul19_v7-1.pdf (accessed on 2 February 2022).

33. South African Health Products Regulatory Authority (SAHPRA). *Interim Variations Addendum for Human and Veterinary Medicines*; SAHPRA: Pretoria, South Africa, 2020. Available online: https://www.sahpra.org.za/wp-content/uploads/2020/10/Interim-Variations-Addendum-for-Human-and-Veterinary-Medicines_-Final.docx.pdf (accessed on 2 February 2022).
34. Ndomondo-Sigonda, M.; Miot, J.; Naidoo, S.; Dodoo, A.; Kaale, E. Medicines Regulation in Africa: Current State and Opportunities. *Pharm. Med.* 2017, *31*, 383–397.
35. Australian Government, Department of Health Therapeutic Goods Administration (TGA). *Evidence of GMP for Pre-Scription Medicines*; TGA: Woden, Australia, 2019. Available online: https://www.tga.gov.au/evidence-gmp-prescription-medicines (accessed on 2 February 2022).
36. Australian Government, Department of Health Therapeutic Goods Administration (TGA). *Colourings Used in Medicines for Topical and Oral Use*; TGA: Woden, Australia, 2018. Available online: https://www.tga.gov.au/publication/colourings-used-medicines-topical-and-oral-use (accessed on 2 February 2022).
37. Australian Government, Department of Health Therapeutic Goods Administration (TGA). *Guideline for the Labelling of Medicines*; TGA: Woden, Australia, 2014. Available online: https://www.tga.gov.au/sites/default/files/consult-labelling-medicines-140822-guideline.pdf (accessed on 2 February 2022).
38. Australian Government, Department of Health Therapeutic Goods Administration (TGA). *Australian Register of Therapeutic Goods*; TGA: Woden, Australia, 2019. Available online: https://www.tga.gov.au/australian-register-therapeutic-goods (accessed on 2 February 2022).
39. Government of Canada. *Food and Drug Regulations (C.R.C., c. 870) Part C.01.001*; Government of Canada: Ottawa, ON, Canada. Available online: https://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/page-1.html (accessed on 2 February 2022).
40. Health Canada. *Guidance Document: Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions*

(ANDSs); Health Canada: Ottawa, ON, Canada, 2018. Available online: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/notice-quality-chemistry-manufacturing-guidance-new-drug-submissions-ndss-abbreviated-new-drug-submissions.html (accessed on 2 February 2022).

41. Health Canada. *Labelling of Pharmaceutical Drugs for Human Use*; Health Canada: Ottawa, ON, Canada, 2015. Available online: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/updates-guidance-document-labelling-pharmaceutical-drugs-human-use.html (accessed on 2 February 2022).
42. Health Canada. *International Council for Harmonisation (ICH)*; Health Canada: Ottawa, ON, Canada, 2021. Available online: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation.html (accessed on 2 February 2022).
43. Fatima, B.; Ladislav, N. Artificial sweeteners and sugar substitutes: Some properties and potential health benefits and risks. *Res. J. Pharm. Biol. Chem. Sci.* 2014, *5*, 638–649.
44. Ivanovska, V.; Rademaker, C.M.; Van Dijk, L.; Mantel-Teeuwisse, A.K. Pediatric drug formulations: A review of challenges and progress. *Pediatrics* 2014, *134*, 361–372.
45. Buckley, L.A.; Salunke, S.; Thompson, K.; Baer, G.; Fegley, D.; Turner, M.A. Challenges and strategies to facilitate formulation development of pediatric drug products: Safety qualification of excipients. *Int. J. Pharm.* 2018, *536*, 563–569.
46. Mei, M.; Xu, H.; Wang, L.; Huang, G.; Gui, Y.; Zhang, X. Current practice and awareness of pediatric off-label drug use in Shanghai, China—A questionnaire-based study. *BMC Pediatr.* 2019, *19*, 281.
47. Batchelor, H.K.; Marriott, J.F. Paediatric pharmacokinetics: Key considerations. *Br. J. Clin. Pharmacol.* 2015, *79*, 395–404.

48. National Association of Pharmacy Regulatory Authorities (NAPRA). *Companion to the Model Standards for Pharmacy Compounding of Non-Sterile Preparations*; NAPRA: Ottawa, ON, Canada, 2018. Available online: https://napra.ca/sites/default/files/documents/Mdl_Stnds_Pharmacy_Compounding_Nonsterile_Preparations_Guidance_June2018_FINAL.pdf (accessed on 2 February 2022).
49. Government of Canada. *Forward Regulatory Plan 2021–2023: Amendments to the Food and Drug Regulations—Commercial Compounding*; Government of Canada: Ottawa, ON, Canada. Available online: https://www.canada.ca/en/health-canada/corporate/about-health-canada/legislation-guidelines/acts-regulations/forward-regulatory-plan/plan/regulatory-initiative-amendments-food-drug-regulations-commercial-compounding.html (accessed on 11 February 2022).
50. Salunke, S.; Brandys, B.; Giacoia, G.; Tuleu, C. The STEP (Safety and Toxicity of Excipients for Paediatrics) database: Part 2—The pilot version. *Int. J. Pharm.* 2013, *457*, 310–322.
51. Meyers, R.S.; Thackray, J.; Matson, K.L.; McPherson, C.; Lubsch, L.; Hellinga, R.C.; Hoff, D.S. Key potentially inap-propriate drugs in pediatrics: The KIDs List. *J. Pediatr. Pharmacol. Ther.* 2020, *25*, 175–191.
52. Government of Canada. *Drug and Medical Device Post Market Surveillance*; Government of Canada: Ottawa, ON, Canada. Available online: https://www.canada.ca/en/services/health/drug-health-products/drug-medical-device-highlights-2017/post-market-surveillance.html (accessed on 11 February 2022).
53. Salunke, S.; Tuleu, C. The STEP database through the end-user's eyes—Usability Study. *Int. J. Pharm.* 2015, *492*, 316–331.
54. Challener, C.A. Novel Excipients Needed More Than Ever Before. *Pharm. Technol.* 2021, *45*, 24–29. Available online: https://www.pharmtech.com/view/novel-excipients-needed-more-than-ever-before (accessed on 2 February 2022).

55. Kingwell, K. Excipient developers call for regulatory facelift. *Nat. Rev.* 2020, *19*, 823–824.
56. Elder, D.P.; Kuentz, M.; Holm, R. Pharmaceutical excipients—Quality, regulatory and biopharmaceutical considerations. *Eur. J. Pharm. Sci.* 2016, *87*, 88–99.
57. European Medicines Agency (EMA). *ICH Guideline S11 on Nonclinical Safety Testing in Support of Development of Paediatric Pharmaceuticals Step 5*; EMA: London, UK, 2020; Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-s11-nonclinical-safety-testing-support-development-paediatric-pharmaceuticals-step-5_en.pdf (accessed on 2 February 2022).
58. The People's Republic of China. *Drug Administration Law of the People's Republic of China*; The People's Republic of China: Beijing, China, 2020. Available online: http://www.npc.gov.cn/englishnpc/c23934/202012/3c19c24f9ca04d1ba0678c6f8f8a4a8a.shtml (accessed on 2 February 2022).
59. The China Food and Drug Administration (CFDA). *Chinese Pharmacopoeia*; CFDA: Beijing, China, 2019. Available online: http://wp.chp.org.cn/front/chpint/en/ (accessed on 2 February 2022).
60. National Law Review. *China Amends DMF System on Drug Packaging*; Keller and Heckman LLP: Shanghai, China, 2022. Available online: https://www.natlawreview.com/article/china-amends-dmf-system-drug-packaging (accessed on 2 February 2022).
61. European Commission (EC). *Excipients in the Labelling and Package Leaflet of Medicinal Products for Human Use*; EC: Brussels, Belgium, 2018; Available online: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/guidelines_excipients_march2018_en.pdf (accessed on 2 February 2022).
62. European Medicines Agency (EMA). *Annex to the European Commission Guideline on 'Excipients in the Labelling and Package Leaflet of Medicinal Products for Human Use'*; EMA: London, UK, 2019; Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/annex-

european-commission-guideline-excipients-labelling-package-leaflet-medicinal-products-human_en.pdf (accessed on 2 February 2022).

63. European Medicines Agency (EMA). *Information for the Package Leaflet Regarding Fructose and Sorbitol Used as Excipients in Medicinal Products for Human Use*; EMA: London, UK, 2017; Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/information-package-leaflet-regarding-fructose-sorbitol-used-excipients-medicinal-products-human-use_en.pdf (accessed on 2 February 2022).
64. Christiansen, N. Ethanol exposure through medicines commonly used in paediatrics. *Arch. Dis. Child.* 2015, *100*, 101–104.
65. National Health Service (NHS). *The Truth about Sweeteners*; National Health Service (NHS): London, UK. Available online: https://www.nhs.uk/live-well/eat-well/are-sweeteners-safe (accessed on 2 February 2022).
66. National Health Service (NHS). *Saccharin Link to Cancer Discredited*; National Health Service (NHS): London, UK. Available online: http://www.nhs.uk/Livewell/Goodfood/Pages/the-truth-about-saccharin.aspx (accessed on 2 February 2022).
67. De Schaepdrijver, L.; Mariën, D.; Rhimi, C.; Voets, M.; Van Heerden, M.; Lammens, L. Juvenile animal testing of hydroxypropyl-β-cyclodextrin in support of pediatric drug development. *Reprod. Toxicol.* 2015, *56*, 87–96.
68. European Medicines Agency (EMA). *Questions and Answers on Cyclodextrins Used as Excipients in Medicinal Products for Human Use*; EMA: London, UK, 2013; Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-cyclodextrins-used-excipients-medicinal-products-human-use_en.pdf (accessed on 2 February 2022).
69. O'Brien, F.; Pawar, R.; Upadhaya, P.; Syed, S.; Patravale, V.; Salunke, S. Excipients in parenteral formulations used in Paediatric and neonatal patients: A systematic review. In Proceedings of the 12th EuPFI Virtual Conference, 9–10 September 2020.

70. UNICEF. *Children in India*; UNICEF: New York, NY, USA, 2019; Available online: https://www.unicef.org/india/children-in-india (accessed on 2 February 2022).
71. Nasrollahi, S.; Meera, N.K.; Boregowda, S. Pharmaceutical Excipient Exposure in a Neonatal Intensive Care Unit. *Indian Pediatr.* 2020, *57*, 801–804. World Population Prospects—Population Division. Available online: https://population.un.org/wpp/dataquery (accessed on 2 February 2022).
72. Statista. India-Age Distribution. 2019. Available online: https://www.statista.com/statistics/271315/age-distribution-in-india (accessed on 2 February 2022).
73. Galande, A.D.; Khurana, N.A.; Mutalik, S. Pediatric dosage forms—Challenges and recent developments: A critical review. *J. Appl. Pharm. Sci.* 2020, *10*, 155–166.

APPENDIXES

Appendix A

Міністерство охорони здоров'я України
Житомирський базовий фармацевтичний фаховий коледж
Житомирської обласної ради

Матеріали III Всеукраїнської студентської науково-практичної конференції

«АКТУАЛЬНІ ПИТАННЯ МЕДИКО-БІОЛОГІЧНИХ І ФАРМАЦЕВТИЧНИХ НАУК»

30 березня 2023 року, м. Житомир

УДК 001.89:377.36:615-057.87(477.42)

Рекомендовано до друку педагогічною радою Житомирського базового фармацевтичного фахового коледжу Житомирської обласної ради; протокол № 8 від 27 березня 2023 року.

Укладачки:
Першко І.О., кандидатка біологічних наук, доцентка, голова циклової комісії медико-біологічних дисциплін ЖБФФК;
Новицька М.С., викладачка біологічних дисциплін циклової комісії медико-біологічних дисциплін ЖБФФК.

Актуальні питання медико-біологічних і фармацевтичних наук : матер. III Всеукраїнської студ. наук.-практ. конф., м. Житомир 30 березня 2023 року / за заг. ред. І.Д. Бойчук. Житомир, 2023. 439 с.

Конференцію зареєстровано у Міністерстві освіти і науки України ДНУ УкрІНТЕІ (посвідчення № 405 від 12 вересня 2022 року)

Committee for Human Medicinal Products (CHMP), European Food Safety Authority (EFSA), The Joint FAO/WHO Expert Committee on Food Additives (JECFA), and indexed literature [4].

Additionally, drug-excipient compatibility should be investigated prior to the selection of excipients. Physical, chemical, and biopharmaceutical interactions are considered as the potential interactions between API and excipient. Premature breakdown of enteric coat, interactions due to adjunct therapy (like complex formation between tetracycline and calcium), and increased gastrointestinal motility (because of sorbitol and xylitol) could happen due to unsuitable selection of excipients. Several thermal and nonthermal analysis methods and softwares for incompatibility evaluations are developed, which can further help in proper dosage form preparation.

Reference:

1. Velmurugan S., Vinushitha S. Oral disintegrating tablets: an overview. International Journal of Chemical and Pharmaceutical Sciences . 2010;1(2):1–12.
2. Development and optimization of taste-masked orally disintegrating tablets (ODTs) of clindamycin hydrochloride. Drug Development and Industrial Pharmacy . 2015;41(7):1156–1164. doi: 10.3109/03639045.2014.935392.
3. European Pharmacopoeia . 10. Strasbourg: C.o. E; 2019.
4. Ghosh T., Ghosh A., Prasad D. A review on new generation orodispersible tablets and its future prospective. International Journal of Pharmacy and Pharmaceutical Sciences . 2011;3(1):1–7.

PECULIARITIES OF CREATING PEDIATRIC MEDICINES

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Creating pediatric drugs is highly relevant because children have unique medical needs that differ from adults. They require medications that are specifically formulated and dosed to ensure safety and effectiveness for their developing bodies.

Children's bodies are still growing and developing, and their metabolism, immune system, and organ function can differ from adults. Therefore, a drug that is safe and effective for an adult may not be appropriate for a child, and may even cause harm.

In addition, some diseases and conditions that affect children are different from those that affect adults, which means that the medications used to treat them must also be different. For example, certain cancers, rare genetic disorders, and infectious diseases are more common in children than in adults.

Furthermore, clinical trials for drugs are typically conducted in adults, which means that there may be limited data on how a drug works in children. Without pediatric clinical trials, it can be difficult for doctors to know the best way to prescribe medications for children.

Therefore, creating pediatric drugs is essential to ensuring that children receive the most appropriate and effective medications for their specific medical needs. It can help improve their quality of life, reduce side effects, and save lives [1].

Excipients are inactive ingredients that are added to medications to help with their formulation, stability, taste, and appearance. When formulating pediatric drugs, excipients need to be carefully selected to ensure that they are safe for use in children and do not interfere with the efficacy of the drug.

The excipients used in pediatric medicines must meet specific criteria, such as being non-toxic, non-irritating, and having no known interactions with the active ingredients in the drug. They must also be suitable for the child's age, weight, and developmental stage.

Some common excipients used in pediatric medicines include:

Sweeteners: These are used to improve the taste of the medicine and make it easier for children to swallow. Examples include sucrose, fructose, and sorbitol.

Flavorings: These are used to mask the unpleasant taste of the medicine and make it more palatable. Examples include artificial fruit flavors and vanilla.

Colorants: These are used to make the medicine more visually appealing and easier to distinguish from other medications. Examples include FD&C dyes and titanium dioxide.

Preservatives: These are used to prevent microbial growth and ensure the medicine remains stable over time. Examples include sodium benzoate and propylene glycol.

Bulking agents: These are used to increase the volume of the medicine, making it easier to measure and administer. Examples include lactose and microcrystalline cellulose.

Lubricants: These are used to reduce friction and prevent sticking during the manufacturing process. Examples include magnesium stearate and talc [2].

It is important to note that the use of excipients in pediatric medicines must be carefully considered, and the amount and type of excipients used must be appropriate for the specific drug and child's needs. The safety and efficacy of the excipients should be established through rigorous testing, and their use should be monitored closely in clinical trials and post-market surveillance.

It is therefore essential that all components used in the pharmaceutical manufacturing process and not just the active ingredients, must be assessed and tested to full monograph specifications. Limited testing such as a simple ID may not be adequate and may present a risk. A more recent example is the issue with Sartans, where there is evidence that recycled solvents containing NDEA or NDMA are a source of contamination.

Reference:

1. European Medicines Agency (EMA). Guideline on Pharmaceutical Development of Medicines for Paediatric Use; EMA: London, UK, 2013; Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-development-medicines-paediatric-use_en.pdf (accessed on 2 February 2022).
2. Belayneh, A.; Tadese, E.; Molla, F. Safety and biopharmaceutical challenges of excipients in off-label pediatric formulations. Int. J. Gen. Med. 2020, 13, 1051–1066.

PROSPECTS FOR THE DEVELOPMENT OF A MEDICINAL PRODUCT WITH MACLURA EXTRACT

***Ziyani Chaimae**, student*
***I. Kovalevska**, Doctor of Science (Pharmacy), professor*
National University of Pharmacy, Kharkiv, Ukraine
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Maclura pomifera L. (Maclura aurantiaca Syn., Moraceae family) is a native southwestern American plant commonly known as Osage orange. Osage orange typically grows in sunny areas and can grow in a wide range of soil conditions. Worldwide, various Maclura species are used in folk medicine. Native Americans used M. pomifera for the treatment of cancer. In Bolivia, the plant sap is used for the treatment of tooth pain, and the bark and leaves are used for uterine hemorrhage. Comanche Indians in North America used the Osage orange roots decoction to treat sore eyes. The extract obtained from the fruit, leaves, and

Ф А 2.2.1-32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of Industrial Technology of Drugs
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
of Technologies of
Pharmaceutical
Preparations

_____
Olena RUBAN
"_15_" __of May__ 2022

ASSIGNMENT
FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Ibn Ghazala MONSIF

1. Topic of qualification work: «Development of the composition and technology of antiallergic syrup», supervisor of qualification work: Inna Kovalevska, Doctor of Science (Pharmacy), professor, approved by order of NUPh from "06th" of February 2023 № 35

2. Deadline for submission of qualification work by the applicant for higher education: april 2023.

3. Outgoing data for qualification work: requirements of national pharmacopoeias for pediatric preparations, the technology of pediatric drugs, excipients used in the technology of pediatric preparations.

4. Contents of the settlement and explanatory note (list of questions that need to be developed): literature review, objects and methods, experimental part, references

5. List of graphic material (with exact indication of the required drawings):

tables – 4, pictures – 3

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Inna Kovalevska, professor of higher education institution of department Industrial Technology of Drugs	20.05.2022	20.05.2022
2	Inna Kovalevska, professor of higher education institution of department Industrial Technology of Drugs	15.12.22 - 21.01.2023	15.12.22 - 21.01.2023
3	Inna Kovalevska, professor of higher education institution of department Industrial Technology of Drugs	18.02.2023	18.02.2023

7. Date of issue of the assignment: «15» May 2022.

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Literature review	September	**Done**
2.	Experiment planning	October	**Done**
3.	Experiment execution	November-February	**Done**
4.	Processing of results	March- April	**Done**
5.	Submission to EC	April	**Done**

An applicant of higher education _____ Ibn Ghazala MONSIF

Supervisor of qualification work _____ Inna KOVALEVSKA

ВИТЯГ З НАКАЗУ № 35
По Національному фармацевтичному університету
від 06 лютого 2023 року

нижченаведеним студентам 5-го курсу 2022-2023 навчального року, навчання за освітнім ступенем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація, освітня програма – фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців та 3 роки 10 місяців), які навчаються за контрактом, затвердити теми кваліфікаційних робіт:

Прізвище студента	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі заводської технології ліків**				
Ібн Газала Монсіф	Аналіз вимог нормативної документації різних країн щодо складу педіатричних лікарських засобів	Analysis of requirements of regulatory documentation of different countries regarding the composition of pediatric medicines	проф. Ковалевська І.В	доц. Семченко К.В.

Підстава: подання декана, наказ ректора

Ректор

Вірно. Секретар

Ф А2.8-47-110

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу

щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

№ 112818 від « 1 » травня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Ібн Газала Монсіф, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Аналіз вимог нормативної документації різних країн щодо складу педіатричних лікарських засобів / Analysis of requirements of regulatory documentation of different countries regarding the composition of pediatric medicines», Комісія з академічної доброчесності дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,

професор **Інна ВЛАДИМИРОВА**

0%

31%

Ф А 2.2.1-32-353

REVIEW

for qualification work of the master`s level of higher educftion, specialty 226 Pharmacy, industrial pharmacy

Ibn Ghazala MONSIF

on the topic: « Analysis of requirements of regulatory documentation of different countries regarding the composition of pediatric medicines».

Relevance of the topic. A major hurdle in pediatric formulation development is the lack of safety and toxicity data on some of the commonly used excipients. While the maximum oral safe dose for several kinds of excipients is known in the adult population, the doses in pediatric patients, including preterm neonates, are not established yet due to the lack of evidence-based data.

Practical value of conclusions, recommendations and their validity.

It was determined that a harmonized guideline with clearer safety limits and quantitative information on excipients of concern for the pediatric population for each country or region would be needed. It has been established that internationally harmonized processes for the regulation of excipients can contribute to the provision of safe drug treatment for children.

Assessment of work. The successful solution of tasks enabled the author of the qualification work to achieve the goal and obtain practical and theoretical results. The work was done at a sufficient scientific level, which indicates the author's ability to work with literary sources, analyze, systematize and generalize the experimental data obtained.

General conclusion and recommendations on admission to defend. The qualification work of Ibn Ghazala Monsif meets all the requirements for qualification

works and can be presented for defense at the Examination Commission of the National University of Pharmacy.

Scientific supervisor _____ Inna KOVALEVSKA

«05» April 2023.

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master`s level of higher educftion, specialty 226 Pharmacy, industrial pharmacy

Ibn Ghazala Monsif

on the topic: «Development of the composition and technology of antiallergic syrup».

Relevance of the topic. Pediatric patients have different requirements compared to adults, regarding pharmacotherapy. Flexible dosing, appropriate excipients, ease of administration, and dosage form acceptability or palatability are some of the key parameters for developing formulations appropriate for different age groups of the pediatric subset. Pharmaceutical excipients are no longer considered inert in general, as new evidence suggests that there may be safety concerns with some excipients when used in products for the pediatric population, especially with younger age groups.

Theoretical level of work. The author has analyzed the requirements of the pharmacopoeias of Europe and the United States of America for pediatric drugs and excipients.

The author's suggestions on the topic of research. It was determined that a harmonized guideline with clearer safety limits and quantitative information on excipients of concern for the pediatric population for each country or region would be needed. It has been established that internationally harmonized processes for the regulation of excipients can contribute to the provision of safe drug treatment for children

Practical value of conclusions, recommendations and their validity. Established to provide evidence-based regulation of excipients, collect evidence-based data on

the safety of excipients in the pediatric population, collect information on currently used excipients in pharmaceutical products, including quantitative information, and share current issues of excipient exposure in pediatric patients from all stakeholders, including regulators in each country or region, is mandatory. In addition, harmonized guidance will be required with clearer safety margins and quantitative information on excipients of concern in the pediatric population for each country or region. Internationally agreed excipient regulatory processes can help ensure safe drug treatment in the pediatric population.

Disadvantages of work. There are incorrect expressions and grammatical errors in the work.

General conclusion and evaluation of the work. The qualification work of Ibn Ghazala Monsif based on the results of research and the volume of the experiment performed can be presented for defense at the Examination Commission of the National University of Pharmacy.

Reviewer _____ assoc. prof. Kateryna SEMCHENKO

«10» April 2023

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'ЯУКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ВИТЯГ З ПРОТОКОЛУ № 9

« 21 » квітня 2023 року

м. Харків

засідання кафедри

заводської технології ліків

ПРИСУТНІ: проф. Рубан О.А., проф. Бобрицька Л.О., проф. Гриценко В.І., доц. Хохлова Л.М., доц. Сліпченко Г.Д., проф. Ковалевська І.В., доц. Криклива І.О, ас. Пономаренко Т.О., лаборанти та аспіранти.

ПОРЯДОК ДЕННИЙ:

1. Обговорення кваліфікаційних робіт щодо їх представлення до захисту в Екзаменаційній комісії НФаУ.

СЛУХАЛИ: здобувача вищої освіти 5 курсу групи Фм18(4,10)англ-2 Ібн Газала Монсіф про представлення до захисту в Екзаменаційній комісії НФаУ кваліфікаційної роботи на тему: «Аналіз вимог нормативної документації різних країн щодо складу педіатричних лікарських засобів». (Керівник: д.фарм.н., професор Інна КОВАЛЕВСКА).

В обговоренні кваліфікаційної роботи брали участь проф.Бобрицька Л.О., доц. Хохлова Л.М., доц. Сліпченко Г.Д.

УХВАЛИЛИ: рекомендувати до захисту в Екзаменаційній комісії НФаУ кваліфікаційну роботу здобувача вищої освітифакультету з підготовки іноземних громадянгрупи Фм18(4,10д)англ-1 Ібн Газала Монсіф на тему: «Аналіз вимог нормативної документації різних країн щодо складу педіатричних лікарських засобів».

Голова
Завідувачка кафедри ЗТЛ **Олена РУБАН**

Секретар **Тетяна ПОНОМАРЕНКО**

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ

ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Ібн Газала Монсіф до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я
Спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Аналіз вимог нормативної документації різних країн щодо складу педіатричних лікарських засобів».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ /Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Ібн Газала Монсіф у процесі роботи розглянув сучасні вимоги до педіатричних препаратів Фармакопей США та Європи, встановив різницю та спільні показники, виявив недоліки та перспективи удосконалення педіатричних засобів. Автором показано основні підходи до вибору допоміжних речовин у складі лікарських засобів, що застосовуються у педіатрії. Ібн Газала Монсіф допускається до захисту даної кваліфікаційної роботи у Екзаменаційній комісії Національного фармацевтичного університету.

Керівник кваліфікаційної роботи

_____ Інна КОВАЛЕВСКА

«05» квітня 2023 року

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Ібн Газала Монсіф допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувачка кафедри

заводської технології ліків

_____ Олена РУБАН

« 21» квітня 2023 року

Qualification work was defended

of в Examination commission on

« __ » _____2023 г.

With the grade_____

Head of the State Examination commission,

DPharm Sc. Professor

_____ / Oleg SHPYCHAK /