

EXCIPIENTS FOR PAEDIATRIC POPULATION—SHARED ISSUES NEED UNIFIED SOLUTION

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Abstract

A major hurdle in pediatric formulation development is the lack of safety and toxic 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. This article covers the current state, challenges, ongoing efforts and future perspectives on excipients for pediatric formulation in each country and region. As a common issue, lack of information and insufficient regulation process were found. Efforts such as raising issues on excipient exposure, building the database for excipients and improving excipients regulation process are in progress, however, there is a lack of evidence-based information on safety of excipients for the pediatric population. Some guidelines regarding excipient usage in pediatric formulations in some region or country are available but a harmonized guideline with more clear safety limits and quantitative information on excipients of concern in the pediatric population is needed. Internationally harmonized excipients' regulatory process may contribute to ensuring safe medicinal treatment for the pediatric population.

Keyword list: Excipients, pediatric patients, age-appropriate dosage form.

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Introduction

Pediatric patients have different requirements compared to adults regarding pharmacotherapy^[1]. Key formulation parameters for the development of age-appropriate dosage forms regardless of the location of the proposed patient population include flexible dosing, acceptable excipients, easy product administration and acceptable palatability^[2]. Although excipients are generally considered to be inert, new evidence suggests that there may be safety issues with some excipients when used in products for pediatric patients^[3,4]. For example, immature metabolic

systems in neonates and infants can lead to the accumulation and toxicity of propylene glycol^[5], benzoic acid and benzoates^[6], and these excipients should be used with caution in noticeably young patients such as preterm neonates. Flavoring agents may be included to improve the taste of an oral product and facilitate patient acceptability and adherence, however, there are concerns regarding the potential risk of allergy and sensitization with these materials^[7].

One of the major hurdles in the development of pediatric formulation is the lack of safety and toxicity data on some of the commonly used excipients. Many excipients have no available safety data to support their use in the pediatric population or there is not enough data available to justify their use during regulatory approval of the drug product. While the maximum oral safe dose for several kinds of excipients is known in the adult population^[8,9], the acceptable excipient level in pediatric patients including preterm neonates have not been established yet due to the lack of evidence-based data^[5], and the guidance or recommendation on excipients use for pediatric population vary by countries around the world.

This article summarizes country-specific perspectives including:

- Current state on the safety assessment of pharmaceutical excipients in formulations both for 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



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pediatric population through the pediatric drug development in Japan, USA, Europe, India, Canada, Africa and China.

Country-specific perspectives and ongoing efforts

Japan

In Japan, an assessment for the precedence of excipients use can be made by referring to the Japanese Pharmaceutical Excipients Dictionary (JPED) which is edited by the Japan Pharmaceutical Excipients Council in conjunction with the Ministry of Health, Labor and Welfare (MHLW). The JPED is a compilation of all excipients for which there is a precedence of use in drug products in Japan. The pharmaceutical product application is submitted to the regulatory authorities by the pharmaceutical company typically containing all relevant details concerning the excipient. The data in each monograph have only the safety data including maximum dosage of pharmaceutical excipients for the adult population and there is no evidence-based data for the pediatric population. Additionally, not all excipients reach these texts due to companies withholding data because of concerns about releasing proprietary information. The Drug Master File (DMF) system allows the manufacturers of new excipients to submit the detailed information (manufacturing methods, data, etc.) of excipients to the Review Authority (Japan's Pharmaceuticals and Medical Devices Agency, PMDA). The PMDA uses the available information from the DMF to approve finished drug applications.

Regarding the accessibility of excipients information in the pharmaceutical products, the package inserts must list all ingredients used as excipients. When excipients listed in the JP, in the Minimum Requirements for Biological Products, or the Radiopharmaceutical Standards are used in products, the names and quantities of these excipients must be included in the relevant package inserts. If safety problems are considered to be caused by excipients that have appeared, the names and quantities of excipients must be included in the relevant package inserts^[10]. However, this criterion is not always focused on the safety of pediatric patients. All ingredients as a rule, except for the ingredients stipulated in the MHLW Notification^[11] shall be included in the package insert because of the social responsibility to disclose as much information as possible related to drugs as life-related products. In accordance with 'Guideline for Descriptions on Application Forms for Marketing Approval of Drugs, etc. under the Revised Pharmaceutical Affairs Law'^[12], there is no obligation to indicate quantitative information on the contents of excipients included in the enteral product except for the high-risk excipients such as ethanol, because these products were not developed with the intention of neonatal and/or pediatric administration. Furthermore, in enteral products, contained flavors are not specified. In parenteral products, quantitative information on the contained excipients is sometimes available, however, some of the general excipients such as pH buffering agents and isotonic agents are not disclosed. Furthermore, there is no evidence-based information on the safety of excipients and no beneficial guideline for excipient selection is available.

USA - Food and Drug Administration (FDA)

The FDA's excipient guidance is largely based on the International Pharmaceutical Excipients Council (IPEC) recommendations. The FDA guidance discusses safety testing generally required to establish the safety of a new excipient, which is similar to those required for a new drug^[13]. However, unlike drugs, excipients are designed to be pharmacologically inactive. Currently, DMF systems for excipients exist in the US to support drug product applications.

The IPEC-Americas Master File Guide is an industry guide that can be used to format uniform excipient information for DMF submissions^[13]. The regulatory authority states 'excipients to be used in formulations for the pediatric population should be selected based on thorough risk assessment and possible sensitivities of the different age groups should be taken into consideration'^[14], however, due to the off-label use of pharmaceutical products for pediatric patients including neonates, a safety assessment of these excipients to pediatric population has not been conducted.

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 that may cause hypersensitivity or other adverse reactions shall be included in the label along with the amount. If a drug contains one or more inactive ingredients that may be associated with a significant safety concern in pediatric patients, the risk must be described in labeling^[15].

As an open information database for pharmaceutical excipients, the Inactive Ingredient Database (IID) provides information on inactive ingredients (excipients) present in FDA-approved drug products. In this database, the maximum potency of each excipient per unit dose is available including enteral formulation. FDA will refuse to receive a new drug application if the submission proposes to use an inactive ingredient at a level that exceeds any of the IID listings without justification. However, this database 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 the potential to cause any harmful effects due to patient age; so, additional studies or presence of use in same age group with similar use duration may be needed to justify use of such excipients in pediatric products.

Europe - EMA

The European Commission (EC) published a guideline on 'Excipients in the labeling and package leaflet of medicinal products for human use'. The updated guideline lists out excipients that have a known action or effect which must appear on the labeling of all medicines in the European Union (EU)^[16]. The annex also includes the safety information that must appear in the medicine's package leaflet for the listed excipients.

About 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 in active substances to be included in the package leaflet^[17]. The following applies to the names of all excipients on the labeling, package leaflet and the Summary of Product Characteristics (SmPC).

For information on safety for excipients, the EMA proposed safety limits for several excipients in the pediatric population such as propylene glycol^[18] and sorbitol^[19]. In January 2014, the EMA proposed the inclusion of more detailed information on alcohol content in patient information leaflets (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'^[20,21]. Regarding the novel excipients such as hydroxypropyl- β -cyclodextrin, there is insufficient safety data in pediatric patients, especially in neonates^[22].

As an available database, the Safety and Toxicity of Excipients for Pediatrics (STEP) database is a user-designed free resource that compiles the safety and toxicity information of excipients that is

manually extracted from selected information sources^[23-25]. Further effort is required by the sponsors to share, either voluntarily or upon request, non-confidential in-house data in the STEP database, to allow the users access to a much larger data pool and prevent the repetition of several toxicity studies.

India

Considering the developing nature of the Indian economy, the availability of pediatric formulations, especially in rural areas, is still a matter of concern. Along with the global pharmaceutical regulatory agencies, the Indian drug regulators have also acknowledged the need for regulation in the Indian pediatric scenario. The accessibility of information on pharmaceutical excipients for products is limited except for drugs in the World Health Organization's (WHO) model formulary for children, the WHO's model list of essential medicines for children and the National List of Essential Medicines. For the domestic approved medicine, the compound name cannot be specified and only the information on the use (kinds) of each excipient (i.e., sweetener, flavoring agent, coloring agent, etc.) are available. The suitability of pharmaceutical dosage forms for pediatric use is restricted majorly because of the potency of actives and the use of numerous excipients that form the bulk materials^[26], thereby making compounding a traditional method of pediatric formulation dispensing.

Auditing and monitoring excipient manufacturing and supply chains are also needed to ensure the production and distribution of optimum quality excipients. This has led to the development of IPECs in different parts of the world since 1991^[27]. IPEC India provides a common, domestic as well as international platform to the manufacturers, distributors, regulators and end-users, through several assessment procedures for pediatric excipients including tiered toxicology testing^[28].

On excipients' use of pharmaceutical products, the quantitative information on excipients was rarely available. Special considerations for use of these excipients based on factors like dose, frequency of administration, age, disease condition and length of treatment, need to be thoroughly considered.

Canada- Health Canada

In Canada, the drug development process is bound by the Canadian Food and Drugs Act (F&D Act) and the Food and Drugs Regulations (F&D Regulations). Within the Food and Drug Regulations, Health Canada refers to excipients as 'non-medicinal ingredients'^[29]. As a regulatory requirement to the Act and Regulations, all non-medicinal ingredients (hereafter referred to as excipients) are listed in the Canadian Product Monograph or Prescribing Information. Excipients are an integral aspect of the formulation which influences the drug product's stability and delivery, but may also have an impact on its safety profile. Typically, a justification for the excipients used in the formulation must be adequately addressed in the drug submission package. Supplementary information will be required in the submission in the case of novel excipients; new contexts of use (e.g., new route of administration); as well as when intended for use in vulnerable populations such as pediatrics^[30].

Health Canada has published guidance documents referencing the appropriate use of excipients, such as *Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submission (ANDSs)*^[30] and *Labelling of Pharmaceutical Drugs for Human Use*^[31]. Canada has also adopted ICH quality and safety guidelines and, as such, adheres to the

recommendations found therein^[32]. It should be noted that the recommendations made by various guidance regarding excipients lack enforcement as the F&D Act and F&D Regulations do not provide binding authority in this area.

Quality evaluations of excipients used in drug formulations conducted by Health Canada are based on the Health Canada Guidance^[30], as well as ICH guidelines for impurity qualification (e.g. ICH Q3, M7). Additional data supporting safety assessments may be requested when needed on a case-by-case basis, referring to the specifications (chemical, analytical) outlined in the various official pharmacopeial monographs such as the EuPFI STEP database for pediatric excipients, USP, or Ph. Eur. (when available).

The general principle for safety evaluation regarding excipients in pediatric formulations is described in ICH E11(R1) and S11, which reflect the general approach at Health Canada. The weight of evidence is based on available information and the requirements for a juvenile animal study for testing excipients are stated in ICH S11^[33].

Nigeria and South Africa

Nigeria, through the National Agency for Food and Drug Administration (NAFDAC), codifies regulations on excipients in several documents: Guidelines for Registration of Pharmaceutical Products (GRPP), Clinical Trials in Pediatric Populations (CTPP), SmPC and PIL; Label Guidance; and Non-nutritive Sweeteners Prohibition in Drug Regulation. The GRPP includes consideration of excipients for children in referring to the WHO Guidelines on development of pediatric medicines: points to consider in the choice of excipients. About the concentration of each excipient, other resources are available for information on acceptable excipients and their concentrations, such as the FDA inactive ingredient guide list and the Handbook of pharmaceutical excipients. In addition, available guidelines should be referenced which discuss particular excipients to be avoided^[34]. Additionally, it allows only colours and flavours permitted by other competent authorities such as the FDA and EMA.

In the case of South Africa, as indicated in the guidelines for professional information for human medicines published by South African Health Products Regulatory Authority (SAHPRA)^[35], full details of the qualitative and quantitative composition in terms of the active substance(s) and excipients where knowledge of which is essential for the proper administration of the medicine, should be provided. This is referred to as the EC Guideline on Excipients in the Labelling and Package Leaflet of Medicinal Products for Human Use published by EMA. For complementary medicines containing alcohol, information about the ethanol content in the medicine should be included following the EC Guidelines^[35].

China

China is currently one of the most promising pharmaceutical markets, and new regulatory requirements are leading to important changes, especially regarding excipients used in drug manufacturing. In 2021, the new China Food and Drug Administration (CFDA) regulations, 'Announcement of the CFDA on Adjusting Matters Concerning the Review and Approval of Active Pharmaceutical Ingredients, Pharmaceutical Excipients and Pharmaceutical Packaging Materials (No. 146, 2021)', promulgated on 23rd November 2021; the approval of pharmaceutical excipients is conducted as a part of a drug product application. Relevant pharmaceutical excipients manufacturers need to submit pharmaceutical excipients filing dossiers (i.e., DMF) to CFDA. The Chinese regulatory authorities

also engaged in an intensive exchange with the US FDA, the respective EU authorities, and the European Directorate for the Quality of Medicines & HealthCare (EDQM). Moreover, China has been a member of the ICH since 2017. The implementation of the ICH guidelines in China is an ongoing process.

Compare and contrast country-specific perspectives

The regulatory process for excipients that are included in the pharmaceutical product is similar, however, the information gaps exist. There are some resources for 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 exist in other regions. The law and process for pediatric drug development may make a difference among the countries and regions.

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 flavouring agents were not specified in the product information. Some colouring 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, however, 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.

Discussion and Conclusion

Excipients are an important component of any pharmaceutical formulation and they will remain so for the foreseeable future. The pharmacopoeias, guidelines and regulations for safety evaluation and use of excipients have an important role to play, especially in the pediatric population. Currently, there is no separate regulatory pathway for safety evaluation or approval of excipients. Excipients are reviewed only as part of a drug product application. Much of the information on manufacturing processes and composition of excipients is generally confidential and, as such, manufacturers of these excipients are hesitant to share this information with customers. There is no regulatory requirement to establish an excipient DMF in the US and the requirements for sharing confidential excipient information vary by region. For example, China has recently instituted submission of excipient dossiers which are similar to DMFs. The information in these dossiers is reviewed as part of the drug application. Europe, on the other hand, does not have a mechanism for submission of excipient DMFs. Manufacturers' SmPCs, package inserts, and PILs may be useful for identifying the excipients in particular medicine and 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 assessment for pediatric patients. Although some excipients were disclosed with quantitative information and the extents

of exposure were evaluated through dedicated investigations, its criteria and evaluation results were ambiguous. Furthermore, because most prescriptions for neonates including preterm neonates are 'off-label'^[36], there is no duty for manufacturers to identify the safety of excipients in these pediatric populations. To resolve this situation, a survey based on real-world prescription data and quantitative risk assessment by academia and clinical healthcare professionals is needed. As shown in several open databases (i.e. STEP database, PharmaCircle, IID), 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 even in these open databases. More clear safety limits and quantitative information on problem excipients in the pediatric population are needed.

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. Preparing the common and harmonized guidelines or guidance for excipients use and its labeling in the package leaflet will be desired. The stakeholders in many countries are confronting common problems. Sharing the issues and hammering out the effective measure is desired.

For the evidence-based excipients 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 on excipients exposure to pediatric patients with all stakeholders including regulatory authorities in every countries or region is needed. Additionally, a harmonized guideline with more clear safety limits and quantitative information on excipients of concern in the pediatric population for each country or region is needed as well. Internationally harmonized excipients' regulatory process may contribute to ensuring safe medicinal treatment for the pediatric population.


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