Primary Packaging Considerations in Developing Medicines for Children: Oral Liquid and Powder for Constitution

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ABSTRACT: The packaging presentation of oral liquid pediatric medicines is a critical step in maintaining chemical and physical stability, compliance, adherence, and proper handling by the target patient population, guardians, caregivers, and health-care professionals. The common packaging presentations for commercial oral liquid pediatric drug products are glass bottle, plastic bottle, sachet, and stick pack configurations. The type of pack presentation selected is driven by the quality target product profile (QTPP) that is designed around the physicochemical properties of the drug substance and the desired drug product suitability for the target population. The QTPP defines the intended use of the drug product, drug product quality criteria, dose strength, dosage form, container closure system, storage conditions, stability criteria, dosing device, shelf life, and attributes affecting the pharmacokinetic characteristics. Oral liquid pediatric formulations are typically prepared from a powder that is constituted at the time of use as a suspension or a solution for single or multiple use depending on the stability of the constituted formulation. Active ingredients with high aqueous solubility can be developed as a powder for oral solution and presented in a bottle for multiple use product and a stick pack, packet, or sachet for single-use product. Active ingredients with low aqueous solubility can be developed as a powder for oral suspension and presented in a bottle for multiple use product and a stick pack or sachet for single-use product. A secondary package may be used in cases where the primary pack failed to provide adequate protection against light degradation. This work will help formulation scientists select the most appropriate pack presentation in the early stages of pediatric clinical development. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:52–62, 2015
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INTRODUCTION

The packaging presentation of oral pediatric medicines is a critical step in maintaining chemical and physical stability, compliance, adherence, and proper handling by the target patient population, guardians, caregivers, and health care professionals. The common packaging presentations for commercial oral pediatric drug products are glass bottle, plastic bottle, sachet, and stick pack configurations. Oral pediatric formulations are divided into two main product categories: (1) a ready-to-use formulation such as a tablet, syrup, solution, or suspension; and (2) a formulation that requires manipulation such as a powder for constitution to a suspension or solution, effervescent tablet, dispersible tablet, bulk oral granules or powder to be sprinkled on food, and sprinkle capsule filled with pellets, granules, or minitablets to mix with food or drink.[1] Examples of sprinkle capsules used as pediatric drug products are Tamiflu® (oseltamivir phosphate) capsules that can be added to a mixture of water and Cherry Syrup or Ora-Sweet® to make a suspension and Sustiva® (efavirenz) that is added to infant formula to make a suspension. Strickley et al.[1] compiled the different oral pediatric medicines that are commercially available as both ready-to-use and manipulated formulations, their compositions, preparation procedures, dosage, and strength. Some examples of commercially available pediatric drug products are Afinitor® Disperz™ (everolimus) tablets for oral suspension; Isentress® (raltegravir) tablet for oral suspension is a preservative-free formulation for single use, which comes in a kit that contains packets of raltegravir and reusable syringes and cups needed to mix and give the medicine; Epaned™ (enalapril maleate) powder for oral solution is preserved for multiuse; Lamisil® (terbinfine HCl) oral granules preservative-free formulation for single use filled into stick packs; Sabril® (vigabatrin) powder for oral solution is a preservative-free single-use formulation filled into sachets; and Buccolam® (midazolam) oromucosal solution is filled into prefilled syringes. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has defined the pediatric population in the following age groups, preterm newborn infants (<37 weeks gestation), term new-born infants (0–27 days), infants and toddlers (28 days to 23 months), children (2–11 years), and adolescents [12–18 years (dependent on region)].[2] Therefore, the type of packaging presentation for oral pediatric medicines is highly dependent on the target age group, type of formulation, stability requirements, occupational hazardous category of the active pharmaceutical ingredient (API), multiple- versus single-use product, dose flexibility, and the level of child proofing required.

In most cases during early development, the developing company has limited initial stability information on the drug

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product in the most appropriate pack presentation and, therefore, is overly conservative on the type of primary pack used for the drug product. For example, because of the lack of photostability, an amber or colored primary pack (vial or bottle) and a customized secondary pack (such a carton box) may be used and continues to be used throughout development and even commercialization. This increases the cost of goods, complicates the supply chain, and adds complexity to both the packaging and labeling operations. In cancer therapy, there are no pediatric-specific medicines and therefore oncology pediatric patients are treated with off-label use drug products that are prepared extemporaneously from solid dosage forms (tablets and capsules).[3] For these off-label preparations, the oral suspension and/or solutions are prepared and stored in amber glass bottles with child-resistant closure, and in some cases where chemical and physical stability data are available the product can be used multiple times.[4,5]

Usually, tablets are packaged in high-density polyethylene bottle (HDPE) with child-resistant closure but for children above 12-year-old tablets can be packaged in a blister pack. Some solid oral dosage forms are moisture sensitive and will be required to be desiccated to maintain stability on storage over its shelf life, for example, Singulair® Chewable tablets.[6] The ready-to-use liquid-based formulations (such as syrup, suspension, and solution) and powder for constitution to a suspension or solution for multiple uses are typically packaged in a glass bottle (amber or clear) with a HDPE child-resistant cap closure to minimize the risk of extractables and leachables from the package container and/or to protect the drug product from light. There is also an increase in flexibility for dose adjustments. Some drawbacks to a glass bottle presentation are their bulkiness, risk of breakage during handling and transportation, glass delamination, weight, and large footprint or storage space. For single-use products that require manipulation such as a powder for constitution, granule or bulk powder for sprinkling on food, and pellets or minitablets to mix in with food or drink, it is cheaper and more convenient for the patient to package these in a stick pack or sachet presentation. Some of the negatives to stick pack and sachet pack presentations are the limitation in the fill quantity and size of the pouch, challenges with sealing of the pack, limited space for labeling, difficulty in adding child proof mechanisms, leaching of labeling ink through nonfoil laminate, generation of large amounts of waste during production, provide a risk of exposure during opening and pouring of the drug product into a suitable container for constitution, and may require a second container for constitution.

Hospitalization of children under 5-years old in the 1970s was a record high because of accidental ingestion of aspirin and paracetamol caused by the lack of child-resistant packaging.[7] This triggered one of the largest investigations into the safety of packaging containers for children medicines and led to the mandate for all children aspirin and paracetamol to be presented in child resistant and/or dark containers by the United States and British health authorities.[7,8] A significant reduction in the hospitalization of children was observed after the implementation of this safety measure.[9,10]

Sam et al.[11] have reported the use of a benefit/risk approach for the selection of a multiple use versus a single use oral liquid for chronic treatment in children of 2–6-years old.[11] The multiple-use oral liquid was packaged in a glass bottle and the single-use oral liquid was packaged in a sachet. They concluded that the multiple dose oral product was favored over the single unit dose product from a patient access, dose flexibility, cost of goods, and ease of use perspective. Stick packs are frequently being used in the emerging markets for fixed dose combination drug products, for example, in the treatment of malaria.[12,13] Chang et al.[14] studied the effects of piroxicam beta-cyclodextrin in sachet and piroxicam tablets in patients with chronic lower back pain and demonstrated that there was a greater improvement in pain scores and disability index in patients that took piroxicam beta-cyclodextrin in sachet.

The intent of this work is to emphasis the importance of primary packaging container for an oral pediatric medicine that is either a ready-to-use solution or suspension, or a solid that is constituted prior to administration. The primary packaging configuration can impact patient compliance and access, adherence, and proper handling of the medicine by the target patient population, guardians, caregivers, and health care professionals. To the current knowledge of the authors, there is no reporting on the considerations for primary packaging for oral pediatric medicines. This information can help formulation scientists select the most appropriate primary package presentation during the early stages of development of oral pediatric medicines and thus shorten the delivery time to patients who are awaiting treatment.

PACKAGING PRESENTATIONS

Bottles

Glass Bottles

Liquid oral dose pediatric products such as syrups, solutions, and suspensions are commonly packaged in glass bottle presentations. Glass containers are considered to be the most inert and impermeable containers when compared with other conventional materials of construction such as plastics. Glass container manufacturing is a complex process with a wide range of glass formulations utilized by individual manufactures. Two main categories of pharmaceutical glass are borosilicate based and soda lime based. Careful thought and consideration should be given when selecting a glass container for oral liquid pharmaceutical products. Guidance on the suitability of pharmaceutical glass can be found in USP <660> (Containers-Glass) and EP 3.2.1 (Glass Container for Pharmaceutical Use). Three main categories of pharmaceutical glass have been established in USP <660> and EP 3.2.1 to assist with classification and correct utilization of glass containers. The three categories are Type I, II, and III glass. Type I glass is borosilicate based; borosilicate formulations contain a major percentage of boric oxide, aluminum oxide, and alkali/alkaline oxides as a base structure and are known to be the least reactive glass composition available. Typical products packaged in Type I glass are parenteral products for injection or products that are alkaline or known to become alkaline throughout the intended shelf life. Type II and Type III glass are soda lime based with Type II being less reactive than type III but slightly more reactive then Type I. Type II glass is commonly used with aqueous products that will remain below pH 7 for the duration of the intended shelf life. Type III glass is routinely used to package dry powders or liquid product that are not shown to be sensitive toward alkali. In addition to the various grades of glass construction, several coating options exist that can be applied to the