AAPS PharmSciTech, Vol. 18, No. 2, February 2017 (© 2016)
DOI: 10.1208/s12249-016-0527-x

Mini-Review

Theme: Pediatric Drug Development and Dosage Form Design
Guest Editors: Maren Preis and Jörg Breitkreutz

Reflection on the Pharmaceutical Formulation Challenges Associated with a Paediatric Investigation Plan for an Off-Patent Drug

Jennifer Walsh[1,2,3]

Received 29 January 2016; accepted 1 April 2016; published online 20 April 2016

Abstract. In Europe, the development of pediatric medicines for new patent protected products is mandatory and applicants are required to submit a Paediatric Investigation Plan (PIP) to the regulatory authorities. The process is voluntary for off-patent medicines and despite the availability of incentives, there is still a huge unmet need for the development of off-patent pediatric medicines. The aim of the EU grant funded "Labeling of Enalapril from Neonates to Adolescents" (LENA) project is to develop a new pediatric dosage form of the off-patent drug enalapril, for the treatment of heart failure in patients aged from birth to 18 years. This article provides an overview of some of the key formulation challenges that were faced during the product development programme and PIP process, including selection of dosage form and excipients, methodology for administration of the product and evaluation of patient acceptability.

KEY WORDS: dosage form design; Paediatric Investigation Plan; pediatrics.

INTRODUCTION

Historically, minimal research has been conducted in the development of medicines for children, partly due to ethical concerns about performing clinical trials in this vulnerable patient group. During infancy and childhood, there are major changes in terms of growth and development of organs and body systems, as well as cognitive and motor skills. Therefore, pediatric patients have different needs to adults in terms of for example dose of active pharmaceutical ingredient (API), and their ability to tolerate certain dosage forms and volumes of liquid (1). This gives rise to added complexity when developing age-appropriate formulations. In order to improve the availability of high quality pediatric medicines, a number of regulations have been adopted. In the USA, there are two key pieces of legislation regarding pediatric research and development; the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), both of which were permanently re-authorised under Title V of the 2012 FDA Safety and Innovation Act (FDASIA). In Europe, there is one regulation (EU Paediatric Regulation; EC No. 1901/2006; EC No. 1902/2006) which came into force in 2007 and applies to both new products (patent protected, under the protection of a Supplementary Protection Certificate (SPC)) and off-patent medicinal products. Pharmaceutical companies developing a product which is covered by intellectual property rights are required to submit a Paediatric Investigation Plan (PIP) to the Paediatric Committee (PDCO) of the European Medicines Evaluation Agency (EMA) soon after completion of human pharmacokinetic studies. The PIP is a plan of proposed studies in children to generate sufficient data for the authorisation of a medicine; pre-clinical studies including juvenile toxicology, clinical studies, and quality studies describing the formulation development of an age-appropriate product. The PIP is reviewed and approved by the PDCO and may be modified at a later date as new information becomes available. All applications for marketing authorisations of patent-protected products as well as applications for variations for a new indication, pharmaceutical form or route of administration, must include the results of the studies described in the agreed PIP, unless the company has a waiver or deferral. The reward for compliance with an agreed PIP is a 6-month extension to the SPC and in order to achieve this, the PIP applicant must comply with all the key measures (studies) and timelines listed in the EMA PIP decision.

Unlike patent-protected products, the preparation and submission of a PIP for an off-patent drug is optional. Applicants who have completed studies in accordance with an approved PIP for a medicine that is no longer covered by an SPC may apply for a Paediatric Use Marketing Authorisation (PUMA). The product must be exclusively

[1] Jenny Walsh Consulting Ltd, BioCity Nottingham, Pennyfoot Street, Nottingham, NG1 1GF, UK.
[2] on behalf of Ethicare GmbH, Haltern am See, Germany.
[3] To whom correspondence should be addressed. (e-mail: jenny@jennywalshconsulting.com)

for use in children, but will benefit from a total of 10 years of market and data protection. Despite this incentive, there is still a huge unmet need for the development of off-patent pediatric medicines and the widespread use of unlicensed and off-label medicines in children remains (2,3).

The formulation of medicines for children requires the specific needs of this patient population to be taken into consideration and key aspects of pharmaceutical development relating to the safety, administration and acceptability of the product must be included in the PIP (4). This article provides an overview of the key formulation challenges faced when preparing a PIP for the off-patent drug enalapril, as part of the "Labeling of Enalapril from Neonates to Adolescents" (LENA) project.

LENA PROJECT

The LENA project (http://www.lena-med.eu/) is funded by EU Grant Agreement 602295 and includes consortium members from seven European countries. The aim of the project is to clinically evaluate the off-patent drug enalapril for the treatment of heart failure in patients aged from birth to 18 years using a new pediatric dosage form, and to generate sufficient data for, and obtain approval of a PUMA for the product.

Enalapril and its maleate salt is an off patent drug that is an angiotensin converting enzyme inhibitor (ACEI) that has well-established medical use having been marketed in Europe and the USA since the early 1980s. It is viewed as a first-line treatment for children with heart failure by the EMA Expert Group Meeting on Pediatric Heart Failure (5). This is despite there currently being no licensed formulation of enalapril available in Europe suitable for use in children or in patients who are unable to swallow conventional tablets or capsules. As a consequence, enalapril is commonly administered via extemporaneous oral preparations in European hospitals (6), whereby crushed tablets are often suspended in water prior to administration. The absence of age-appropriate formulations and use of extemporaneous or manipulated products can lead to inaccurate dosing/dosing errors and lack of chemical and physical stability, with the impact of dosage form manipulation on the actual dose administered and bioavailability often being unknown (7).

In order to help rectify this problem, a key deliverable for Project LENA is therefore the development of an age-appropriate enalapril product that can be easily and safety administered to patients, with the ultimate goal of the project to generate sufficient data for, and obtain approval of a PUMA for the product.

PHARMACEUTICAL FORMULATION CHALLENGES

An initial Quality Target Product Profile (QTPP) based upon available information was defined (Table I) and used as a starting point for pharmaceutical development activities. A number of formulation challenges were faced during the development of the enalapril pediatric product and are discussed below:

- Selection of age appropriate dosage form
- Excipients
- Dose flexibility
- Method of administration
- Patient acceptability

Table I. Initial Quality Target Product Profile for Enalapril Paediatric Drug Product

Quality attribute	Target
Route of administration	Oral
Dosage form	Acceptable for patients aged from birth to <18 years
Dose range	0.02–0.3 mg/Kg body weight[a]
Pharmacokinetics	Immediate release
Palatability	Neutral taste preferred
Shelf life	Minimum of 12 months
Container closure system	Multi-dose
Other	Excipients must be acceptable for the patient population

Excluding identification, assay, impurities and specific dosage form drug product quality criteria and targets
[a] Estimated range, includes dose titration

It was necessary to fully address these aspects in the PIP, and justify and subsequently obtain approval for the proposed formulation and associated development studies from the PDCO.

Selection of Dosage Form

As stated above, one of the aims of the LENA project was to develop a pediatric product which is appropriate for patients aged from birth to 18 years. This was a key challenge since there are significant differences in the physical development and ability to use different dosage forms between children in this wide age range. The selection of a pediatric dosage form should be made on a case-by-case basis and consider the comparative benefits and risks of different pharmaceutical design options (8). Oral dosage forms commonly used for pediatric patients include tablets (non-dispersible and melt/ oro-dispersible), capsules, multi-particulates (granules, sprinkles, powders for constitution, mini tablets) and oral liquids (drops, solutions, syrups, suspensions). The potential advantages and disadvantages of each have been summarised elsewhere and are broadly determined by physico-chemical and microbiological stability, patient acceptability and dose flexibility (8). Three factors that affect the choice of formulation are the properties of the API, the proposed pediatric age group and disease to be treated (9), and were considered during the formulation selection process.

The API is the maleate salt of enalapril, a derivative of two amino-acids, L-alanine and L-proline. It is chemically described as (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenediote salt (1:1) and its empirical formula is $C_{24}H_{32}N_2O_9$. It is a white to off-white crystalline powder with a molecular weight of 492.5 and a melting point of 143–144.5°C. Enalapril maleate is sparingly soluble in water (16–25 mg/mL at 25°C), soluble in ethanol, and freely soluble in methanol (10). In addition, enalapril maleate appears to have poor aqueous stability, and although the API shows appreciable stability at room temperature in the solid state, cyclisation and hydrolysis occur when enalapril maleate is in aqueous solution (11). Indeed, solutions of enalapril maleate in sterile water have been reported to be stable for up to only approximately 2 weeks at room temperature (12) and enalapril tablets must be stored protected from moisture.

Despite oral liquids allowing flexibility and ease of dosing and being considered to be acceptable for the whole pediatric population from birth (1,13), this dosage form was not selected due to the inherent instability of the API in this type of formulation. In line with clinical practice and depending upon the etiology of heart failure, some pediatric patients may require chronic enalapril maleate treatment. Oral liquids often require the inclusion of preservative to maintain their microbiological quality and there are limited data regarding the levels of safe exposure of many preservatives in young children and babies, especially during long-term use (13). Furthermore, a prolonged use of oral liquid medications has been implicated as a risk factor for the development of dental erosion in children, in particular where the pH of the medicine is below pH 5.5 (14,15). It was therefore decided to investigate the use of pediatric solid oral dosage forms.

Enalapril maleate is commonly supplied in the form of tablets for oral administration. The age at which children can swallow tablets depends on the size and shape of the tablet as well as the ability of the child (13). However, since the development programme included patients from birth, it was considered that a conventional tablet dosage form is unsuitable. According to pediatric pharmaceutical development guidelines, powders and granules may be given to patients from birth as long as they are administered as a liquid (13). Although a powder or granules for constitution would overcome some of the challenges around long-term stability of the API in an aqueous environment, since a multi-dose container was required (see Table I), it would still be necessary to include a preservative in the formulation to ensure the microbiological quality of the constituted oral liquid was maintained.

The development and acceptability of mini tablets[1] (from 2 to 4 mm in diameter) in infants and children have been investigated by a number of researchers (16–20). In the studies conducted by Spomer (18) and Klingmann (20), the acceptability of 2-mm diameter coated and uncoated mini tablets was found to be significantly higher compared to 3-mL glucose syrup in children aged 6 months to 6 years (60 and 306 participants respectively). More recently, Klingmann (21) investigated the acceptability of a 2-mm diameter uncoated mini tablet and 0.5 mL glucose syrup in 151 neonates (aged 2–28 days). Both formulations were found to be equally 100% acceptable, whilst swallowability of the uncoated mini tablet was found to be significantly higher than that of the glucose syrup. The mini tablets in these studies were well tolerated indicating this dosage form is suitable for young children. Mini tablets offer the advantages of solid oral dosage forms in terms of ease of transport and storage, the ability to be produced using conventional manufacturing processes and greater stability than liquid and semi-solid formulations. In addition, they offer the opportunity of flexibility of dosing via the administration of individual or multiple mini tablets (22).

[0] Mini tablets are defined as tablets with a diameter of up to 3 mm. van Riet-Nales *et al.* evaluated the acceptability of 4 mm "mini tablets".

Although the most recent study indicated the suitability and acceptability of 2-mm uncoated mini tablets in neonates, there may be a concern regarding the potential risk of choking and/or aspiration in very young children. Oro-dispersible tablets rapidly disintegrate in the mouth into small particles which can be easily swallowed thereby mitigating the choking risk, and have previously been reported as acceptable or very acceptable in 96% of 2–12-year-old patients (23). Oro-dispersible mini tablets (ODMTs) which exhibit similar dimensions to mini tablets but disintegrate quickly upon contact with water (or saliva) have been developed (24,25). ODMTs have the benefits of both mini tablets and oro-dispersible tablets and were therefore selected as the dosage form for the development of the age-appropriate enalapril maleate product.

Justification of Excipients

The excipients selected for inclusion in a pediatric formulation together with their concentration must be justified in the PIP. There are considerable physiological differences between children of different ages and adults (26). In addition, the activity of metabolising enzymes and renal function develop with age (27). Neonates (0–27 days) are especially vulnerable as most organs are physiologically immature in this group of patients (28). Therefore, pediatric patients may not be able to metabolise or eliminate an excipient in the same way as an adult, which could potentially lead to toxicity. Furthermore, excipients may have an effect on developing organ systems (1,13).

A key challenge associated with the justification of excipients is the general paucity of available safety and tolerability information on their use in pediatrics. Indeed, safety data including acceptable daily intake limits tend to be derived from adult exposure. It is therefore necessary to also consider and evaluate animal safety data and precedence of use in other authorised pharmaceutical products and food. The CHMP (13) have provided a useful Points to Consider algorithm for the evaluation of safety profiles of excipients and the EMA has published a number of Question and Answer documents on excipients which have undergone a review as part of the on-going programme of work to update the excipient labelling guideline (29). In addition, the European Paediatric Formulation Initiative (EuPFI) in collaboration with the US Pediatric Formulation Initiative (USPFI) have developed a "Safety and Toxicity of Excipients for Paediatrics" (STEP) database which provides a valuable repository of published information on the safety and toxicity of almost 40 commonly used excipients (30–32). Despite these valuable sources, there is still a lack of robust information available. Excipient groups which have been associated with potential risks include coloring agents, flavors, preservatives, sugars and sweeteners (13) and hence special consideration was given to the need for their inclusion in the pediatric formulation. The minimum number and levels of excipients required to develop ODMTs to achieve the characteristics defined in the QTPP were selected and discussed in the PIP.

It was proposed to utilise direct compression (DC) for the manufacture of the ODMTs since enalapril maleate is highly susceptible to degradation under moderate temperature and humidity (33), and DC is also a relatively low cost

process. Sugar alcohols (polyols) such as mannitol, sorbitol, xylitol and erythritol are commonly used as oro-dispersible tablet excipients since they impart a creamy and sweet mouth feel to the product with a cooling sensation, although they tend to have low compactability (34). Sugar alcohols are considered to be of low toxicity, and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has not established an acceptable daily intake (ADI) for these excipients since it was not deemed necessary as they were not considered to represent a hazard to health. However, sugar alcohols have poor oral absorption and when taken at high doses can have an osmotic laxative effect and potentially influence bioavailability (35). A review of published studies reporting gastrointestinal effects for low digestible carbohydrates including sugar alcohols has estimated ADIs for mannitol, sorbitol, xylitol and erythritol of 20, 30, 30 and 40 g per day, respectively (36). Although the laxation threshold in pediatrics is not known, the very low level of sugar alcohols that would be used in the proposed ODMT product was considered to have negligible gastrointestinal effects. In order to ensure the production of mechanically strong ODMTs with short disintegration times, it was necessary to investigate the feasibility and patient acceptability of various binders and disintegrating agents. The use of co-processed excipients whereby excipients with different functions are combined by blending, spray drying or co-grinding (34) was investigated and found to improve the physical properties of the ODMTs.

Since the ODMTs are a solid dosage form, it was not necessary to include a preservative in the formulation. In order to maximise dosing flexibility, more than one strength of ODMT was required. Due to the very small dimensions of the ODMTs, it was not feasible to utilise embossing or modification of ODMT shape to distinguish between the different strengths and hence it was necessary to apply the use of a coloring agent to avoid accidental dosing errors. Several azo-colors are permitted for use in food in Europe, although a number of cases of intolerance and/or allergic reactions have been historically reported in the literature (for example to Tartrazine, Ponceau 4R, Sunset Yellow and Amaranth). In light of these concerns, a review of recent scientific evidence on the appropriateness of food azo-colors for inclusion in the list of permitted food ingredients in Europe was conducted by the European Food Safety Authority (EFSA) panel on Dietetic Products, Nutrition and Allergies (37). Despite the apparent lack of well-controlled studies, the panel concluded that it is unlikely that the oral consumption of the food colors reviewed, either alone or in combination, would trigger severe allergic reactions at their current levels of use. The EFSA has also conducted a series of assessments of exposure to various food azo-colors based on data usage from industry, analytical data and food consumption data, from which it has been concluded that none of the exposure estimates exceed the food azo-color ADIs in any of the populations evaluated (38–42). It should be noted that the youngest children considered in these evaluations were aged 1 year. Despite the findings of the EFSA, the LENA product development team considered that the use of a small quantity of an iron oxide colorant was preferable to an azo food-color in the proposed pediatric patients, since these compounds appear to have a better safety profile and are regarded as generally non-toxic and non-irritant (43).

Flavoring agents and sweeteners including sugars are commonly used to help taste mask an unpleasant-tasting API and improve a product's palatability. Flavors are often complex mixtures, the exact composition of which is not known, and have been associated with safety concerns including risk of toxicity, allergies and sensitization (44). In order to avoid such issues, a flavoring agent was not included in the proposed formulation. Similarly, since the proposed ODMT sugar alcohol fillers are bulk sweeteners with their own inherent sweetness, an additional sweetening agent was not included. Chronic administration of liquid medications sweetened with sucrose has been found to increase the incidence of dental caries and gingivitis in children (45) and hence the use of cariogenic sweeteners (including sucrose, fructose and glucose) in pediatric products must be justified (13).

Administration Challenges

It is important to ensure the pediatric product can be easily and safely administered to patients, in accordance with clinical requirements. The main challenges associated with the administration of the LENA ODMTs were flexibility of dose and method of administration.

Dose Flexibility

A pediatric formulation should allow sufficient flexibility of dosing to accurately administer the optimal dose to the child (9). This is of particular importance where treatment is not short term and the required dose of API changes as the child grows. When treating patients with ACEIs such as enalapril, at treatment initiation it is recommended to start with a low dose and closely monitor any clinical effects. The dose is usually gradually increased (up-titrated) in accordance with clinical response, until a maintenance dose is reached. Hence, the LENA ODMTs are required to enable flexible dosing to allow both dose titration and adjustment of dose due to changes in a patient's age and body weight. Furthermore, it was necessary to consider the wide age range of patients and the associated likely differences in doses required between the different age groups (see Table I).

In order to overcome this challenge, more than one strength of LENA ODMTs was developed. The identification of suitable ODMT strengths required close collaboration with the LENA pediatric clinical pharmacologists and clinical partners to identify potential dosing schemes which met clinical requirements yet avoided the need for patients to be administered multiples of different ODMTs. The manufacture of ODMTs utilises a rotary tablet press with multiple-tip tooling, and to ensure uniform die filling together with acceptable weight and content uniformity, the powder blend requires good flow (46). In addition, blend homogeneity is particularly important especially for low dose ODMTs. A series of experiments was therefore conducted to determine the feasibility of formulating and manufacturing different ODMT variants to meet clinical needs, and the data generated were used to facilitate the selection of ODMT strengths.

It was recognised that very young patients of low birth weight may require a starting dose of enalapril that is less

than the minimum ODMT strength that could be accurately and consistently manufactured. In order to meet the needs of this small group of patients, a series of investigations was conducted to evaluate the dispersal of the LENA ODMTs in water and the accuracy of measuring and administering various doses via oral syringe.

Method of Administration

A clear and simple method of medicine administration helps reduce the risk of medication errors. For the majority of patients, it is proposed that the ODMTs will be administered by placing them directly in the mouth and allowing them to disintegrate into small particles that can be easily swallowed, or by swallowing whole. Both approaches may be facilitated by the patient taking a beverage of their choice. The ODMTs are not intended to be mixed directly with beverages before swallowing although it has been recognised that caregivers may wish to use this approach to facilitate pediatric medicine administration (13,47,48). It was therefore necessary to evaluate the compatibility and stability (standing time) of the LENA ODMTs with some commonly used beverages. The investigations monitored the appearance, assay of enalapril and related substances (RS) of samples of ODMTs dispersed in beverages over a period of up to 2 h. In order to ensure the enalapril and RS content of the samples could be accurately and consistently determined, it was necessary to undertake additional analytical method development and validation work for each beverage to be tested, which significantly increased the project workload and already limited resource requirements (equivalent to one full time researcher for 2 months).

Oral medicines may be administered to patients who are fed via enteral tube and so it was necessary to investigate the feasibility of administering the LENA ODMTs via nasogastric (NG) tubes (13). It has previously been shown that NG tube length does not appear to significantly influence the transit of a medicinal product through an NG tube; however, both tube diameter and flush volume can have an impact on delivery of the dose administered (49). 6Fr or 8Fr NG tube sizes are commonly used for pediatric patients, but due to their narrow size can become easily blocked with viscous liquids and/or large particles. In addition, consideration needs to be given to patients' daily fluid allowance when determining appropriate administration and flush volumes. The compatibility of the medicinal product with the NG tube material and the method of administration also need to be considered (13,50) and were therefore evaluated as part of the pharmaceutical development studies.

Patient Acceptability

Patient acceptability has been described as an overall ability of the patient and caregiver to use a medicinal product as intended (or authorised) (51). It is likely to have a significant impact on patient adherence and consequently on the safety and efficacy of a medicinal product, and is determined by the characteristics of the product and the user. Palatability is one of the main elements of the patient acceptability of oral pediatric medicines and is defined as the overall appreciation of a medicinal product in relation to its smell, taste, aftertaste and texture (13). The EMA advocates the evaluation of patient acceptability of pediatric products during development, but due to the diversity of approaches and results reported in the literature, the EMA provides no guidance on the method and the acceptance criteria that should be used for such studies. Swallowability has been identified as a key factor that affects the acceptability of tablets in children, with the ability of patients to swallow tablets being strongly related to the size of dosage form as well as the age of the patient (52). Indeed, size and shape have been identified as two of the critical attributes of conventional monolithic solid oral dosage forms which should be evaluated (51). Since oro-dispersible dosage forms are dispersed in the mouth, key factors and critical attributes affecting their acceptability which should be considered during acceptability testing are taste and texture (mouth feel) (51,52), and taste has been the most commonly reported barrier to oral medicine administration, especially for liquids and soluble tablets and powders (48).

It was therefore proposed to evaluate the acceptability of the LENA ODMTs during the pediatric studies via the assessment of swallowability and palatability of the dosage form. Since an internationally harmonised method of assessment has not yet been developed, it was necessary to devise an approach for the LENA studies. A similar methodology as previously successfully used by Klingmann (20,21) for the evaluation of acceptability and swallowability was proposed, whereby deglutition of the ODMTs is observed and the patient's mouth inspected by an investigator to assess any product residue in accordance with the following criteria; "everything swallowed", "partially swallowed/chewed", "spat out", "choked on" or "termination/refused" (discontinued). Palatability assessment is often conducted via the use of questionnaires; however, this approach is challenging in young children as they tend to answer questions to the affirmative. In addition, the use of scaling tests such as hedonic scales is problematic in children younger than 5 years, although it is not known at what age such scales can effectively be used (53). It was therefore necessary to create two methods for collating information on the palatability of the product; one for children aged 5 years and below which recorded facial expressions, and one for those aged 6 years and above which comprised a short and simple questionnaire.

CONCLUSIONS

The formulation of age-appropriate medicines for children has added complexity compared to the development of products intended for adult patients. In the LENA project, the wide age range (0–18 years) of the proposed pediatric population gave rise to further difficulties due to the diversity in the needs and abilities of this group. The key formulation challenge was the selection of an appropriate and acceptable dosage form that contained excipients with suitable safety and tolerability in the proposed pediatric patients, and which would allow sufficient flexibility and ease of dosing. How and when the palatability and acceptability of the selected dosage form could be assessed during the project also needed to be determined.

When developing a pediatric product as part of a PIP, formulators need to be aware of and anticipate potential PDCO requests and build these into the development programme within project time and budget constraints. It

should be remembered that a PIP is a plan of intended studies, together with summaries of available information on for example existing formulations, whilst the data generated during the studies outlined in the PIP must be sufficient in order to fulfil the requirements of a PUMA submission. Close collaboration between partners is vital to the success of a PIP, in particular pediatric clinical pharmacologists and clinicians, to ensure a product that meets the needs of the patients can be developed and supplied in accordance with the agreed PIP key measures and timelines.

COMPLIANCE WITH ETHICAL STANDARDS

Funding The research leading to these results has received funding from the EU's Seventh Framework Programme (FP7/2007–2013) under grant agreement n°602295 (LENA). The author has provided consultancy support to the LENA project, but received no financial support for the creation of this manuscript.

REFERENCES

1. CHMP EMEA, Reflection paper: formulation of choice for the paediatric population. 2006. Available at: http://www.emea.europa.eu/pdfs/human/paediatrics/19481005en.pdf.
2. Kimland E, Odlind V. Off-label drug use in pediatric patients. Clin Pharmacol Ther. 2012;91:796–801.
3. Corny J, Lebel D, Bailey B, Bussieres J-F. Unlicensed and off-label drug use in children before and after pediatric governmental initiatives. J Pediatr Pharmacol Ther. 2015;20:316–28.
4. European Commission Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers and deferrals and concerning the operation of compliance check and on criteria for assessing significant studies. 2014/C 338/01. Available at: http://ec.europa.eu/health/files/eudralex/vol-1/2014_c338_01/2014_c338_01_en.pdf.
5. EMA Report on the Expert Group Meeting of Paediatric Heart Failure, London 29 November 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/04/WC500105356.pdf.
6. EMA Report on the survey of all paediatric uses of medicinal products in Europe (EMA/794083/2009). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101006.pdf.
7. Richey RH, Shah UU, Peak M, Craig JV, Ford JL, Barker CE, *et al*. Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. BMC Pediatr. 2013;13:81.
8. Sam T, Ernest TB, Walsh J, Williams JL. A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms—an application for paediatric dosage form selection. Int J Pharm. 2012;435:115–23.
9. Wang S. Formulations in paediatric investigation plans (PIPs): introduction to PIP quality section and regulatory framework. Int J Pharm. 2015;492:332–4.
10. PubChem Compound Summary for CID 5388961 Enalapril Maleate. Available at: https://pubchem.ncbi.nlm.nih.gov/compound/Enalapril_maleate.
11. Stanisz B. Evaluation of stability of enalapril maleate in solid phase. J Pharm Biomed Anal. 2003;31:375–80.
12. Saulnier L, Schlatter J. Stability of enalapril solutions prepared from tablets in sterile water. Aust J Hosp Pharm. 1997;27(5):395–7.
13. CHMP: Guideline on pharmaceutical development of medicines for paediatric use 2012 (EMA/CHMP/QWP/805880/2012 Rev. 2). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147002.pdf.
14. Taji S, Seow WK. A literature review of dental erosion in children. Aust Dent J. 2010;55:358–67.
15. Xavier AFC, Moura EFF, Azevedo WF, Vieira FF, Abreu MHNG, Cavalcanti AL. Erosive and carcinogenicity potential of pediatric drugs: study of physicochemical parameters. BMC Oral Health. 2013;13:71.
16. Thomson SA, Tuleu C, Wong ICK, Keady S, Pitt KG. Minitablets: new modality to deliver medicines to preschool-aged children. Pediatrics. 2009;123:e235–8.
17. Van de Vijver E, Desager K, Mulberg AE, Staelens S, Verkade HJ, Bodewes FA, *et al*. Treatment of infants and toddlers with cystic fibrosis-related pancreatic insufficiency and fat malabsorption with pancrelipase MT. J Pediatr Gastroenterol Nutr. 2011;53:61–4.
18. Spomer N, Klingmann V, Stoltenberg I, Lerch C, Meissner T, Breitkreutz J. Acceptance of uncoated mini-tablets in young children: results from a prospective exploratory cross-over study. Arch Dis Child. 2012;97:283–6.
19. van Riet-Nales DA, de Neef BJ, Schobben AFAM, Ferreira JA, Egberts TCG, Rademaker CMA. Acceptability of different oral formulations in infants and preschool children. Arch Dis Child. 2013;98:725–31.
20. Klingmann V, Spomer N, Lerch C, Stoltenberg I, Frömke C, Bosse HM, *et al*. Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children. J Pediatr. 2013;163:1728–32.
21. Klingmann V, Seitz A, Meissner T, Breitkreutz J, Moeltner A, Bosse HM. Acceptability of uncoated mini-tablets in neonates—a randomized controlled trial. J Pediatr. 2015;167:893–6.
22. Tissen C, Woertz K, Breitkreutz J, Kleinebudde P. Development of mini-tablets with 1 mm and 2 mm diameter. Int J Pharm. 2011;416:164–70.
23. Rancé F, Deslandes B, Decosta P. Acceptability and tolerance of prednisolone metasulfobenzoate in orally dispersing tablets in 2 to 12-year-old children. Arch Pediatr. 2004;11:1127–30.
24. Stoltenberg I, Breitkreutz J. Orally disintegrating mini-tablets (ODMTs)—a novel oral dosage for paediatric use. Eur J Pharm Biopharm. 2011;78:462–9.
25. Hermes. Kindgerechte, niedrigdosierte Zubereitung mit Enalaprilmaleat. 2012. Göttingen: Cuvillier Verlag. Available at: http://www.cuvillier.de/flycms/en/html/30/-UickI3zKPS3xcE0=/Buchdetails.html.
26. Kaye JL. Review of paediatric gastrointestinal physiology data relevant to oral drug delivery. Int J Clin Pharm. 2011;33:20–4.
27. Strollin-Benedetti M, Whomsley R, Baltes EL. Differences in absorption, distribution, metabolism and excretion of xenobiotics between the paediatric and adult populations. Expert Opin Drug Metab Toxicol. 2005;1:447–71.
28. CHMP: Guideline on the investigation of medicinal products in the term and preterm neonate. 2009. (EMEA/536810/2008). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003750.pdf.
29. EC 2003 NOTICE TO APPLICANTS VOLUME 3B Guidelines Medicinal products for human use Safety, environment and information Excipients in the label and package leaflet of medicinal products for human use July 2003. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003412.pdf.
30. Salunke S, Giacoia G, Tuleu C. The STEP (Safety and Toxicity of Excipients for Paediatrics) database. Part I—a need assessment study. Int J Pharm. 2012;435:101–11.
31. 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;457:310–22.
32. Salunke S, Tuleu C. The STEP database through end-users eyes—USABILITY STUDY. Int J Pharm. 2015;492:316–31.
33. de Diego M, Godoy G, Mennickent S, Godoy R. Chemical stability of enalapril maleate drug substance and tablets by a stability-indicating liquid chromatographic method. Quim Nova. 2011;34(3):450–4.
34. Al-khattawi A, Mohammed AR. Compressed orally disintegrating tablets: excipients evolution and formulation strategies. Expert Opin Drug Deliv. 2013;10(5):651–63.

35. Chen M-L, Sadrieh N, Yu L. Impact of osmotically active excipients in bioavailability and bioequivalence of BCS class III drugs. AAPS J. 2013;15(4):1043–50.
36. Grabitske HA, Slavin JL. Gastrointestinal effects of low-digestible carbohydrates. Crit Rev Food Sci Nutr. 2009;49(4):327–60.
37. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific opinion on the appropriateness of the food az-colours Tartrazine (E102), Sunset Yellow FCF (E110), Carmoisine (E122), Amaranth (E123), Ponceau 4R (E124), Allura Red AC (E129), Brilliant Black BN (E151), Brown FK (E154), Brown HT (E155) and Litholrubine BK (E180) for inclusion in the list of food ingredients set up in Annex IIIa of Directive 2000/13/EC. EFSA J. 2010;8(10):1778.
38. EFSA Panel on Dietetic Products, Nutrition and Allergies. Scientific opinion on the re-evaluation Tartrazine (E102). EFSA Journal. 2009;7(11):1331.
39. EFSA. Refined exposure assessment for Amaranth (E123). EFSA J. 2013;11(10):3442.
40. EFSA Panel of Food Additives and Nutrient Sources added to Food. Reconsideration of the temporary ADI and refined exposure assessment for Sunset Yellow FCF (E110). EFSA J. 2014;12(7):3765.
41. EFSA. Refined exposure assessment for Allura Red AC (E129). EFSA J. 2015;13(2):4007.
42. EFSA. Refined exposure assessment for Ponceau 4R (E124). EFSA J. 2015;13(4):4073.
43. Egger C, Schoneker D, Tiwari S. Iron oxides. In: Rowe RC, Sheskey PJ, Cook WG, Fenton MW, editors. Handbook of pharmaceutical excipients. London: Pharmaceutical Press; 2012. p. p389–90.
44. Walsh J, Cram A, Woertz K, Breitkreutz J, Winzenburg G, Turner R, *et al*. Playing hide and seek with poorly tasting paediatric medicines: do not forget the excipients. Adv Drug Deliv Rev. 2014;73:14–33.
45. Roberts IF, Roberts GJ. Relation between medicines sweetened with sucrose and dental disease. BMJ. 1979;2:14–6.
46. Aleksovski A, Dreu R, Gasperlin M, Planinsek O. Mini-tablets: a contemporary system for oral drug delivery in targeted patient groups. Expert Opin Drug Deliv. 2015;12:65–84.
47. van Riet-Nales DA, Ferreira JA, Schobbena AFAM, de Neef BJ, Egberts TCG, Rademaker CMA. Methods of administering oral formulations and child acceptability. Int J Pharm. 2015;492:261–7.
48. Venables R, Batchelor H, Hodson J, Stirling H. Determination of formulation factors that affect oral medicines acceptability in a domiciliary paediatric population. Int J Pharm. 2015;480:55–62.
49. Ponrouch MP, Sautou-Miranda V, Boyer A, Bourdeaux D, Montagner A, Chopineau J. Proton pump inhibitor administration via nasogastric tube in pediatric practice: comparative analysis with protocol optimization. Int J Pharm. 2010;390:160–4.
50. Ruzsikova A, Souckova L, Suk P, Opatrilova R, Kejdusova M, Sramek V. Quantitative analysis of drug losses administered via nasogastric tube—in vitro study. Int J Pharm. 2015;478:368–71.
51. Kozarewicz P. Regulatory perspectives on acceptability testing of dosage forms in children. Int J Pharm. 2014;496:245–8.
52. Liu F, Ranmal S, Batchelor HK, Oru-Gul M, Ernest TB, Thomas IW, *et al*. Patient-centred pharmaceutical design to improve acceptability of medicines: similarities and differences in paediatric and geriatric populations. Drugs. 2014;74:1871–89.
53. Mennella JA, Beauchamp GK. Optimizing oral medications for children. Clin Ther. 2008;30:2120–32.