



Editorial

Paediatric Medicines: Formulation Considerations

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ABSTRACT

The use of unlicensed and off-label medicines in children is widespread and has raised an increasing concern over the last years. The majority of medicines taken by children are extemporaneously compounded by pharmacist, and there is a lack of information regarding bioavailability, suitability and stability. These formulations must be prepared from pure active substance and not from commercially available dosage forms. The development of paediatric formulations, particularly those suitable for very young children, can be a challenge to pharmacists. There is limited knowledge available about the acceptability of different dosage forms, administration volume, dosage form size, taste, safety of formulation excipients regarding to age and development status. The selection of formulation and route of administration depends on the disease being treated and the clinical condition. European Guidelines and reflection papers recommend that pharmaceutical development should consider some parameters like capability, acute or long-term illness, caregiver convenience, disability, culture differences and formulations more attractive to children must be explored.

EDITORIAL**A lack of medicines for children and the impact of paediatric Regulation after ten years of publication**

Throughout many years there were no incentives for the investigation of paediatric medicines and the clinical trials during new drugs development included only adults leading to the lack of medicines well studied in children. In 2002 the European commission published the document "Better Medicines for children", alerting for the needs of developing medicines adequate to paediatric population [1]. However, only in 2007 was published the Regulation (EC) No 1901/2006, whose main objective is lead to the development of new drugs for paediatric use, with the introduction of "Paediatric Investigation Plans" during the development of new drugs, and with incentives to study in children the authorized products for adults no longer covered by intellectual property rights through the Paediatric Use Marketing Authorization (PUMA) [2]. The main goal of this regulatory measures is to ensure the efficacy, safety and tolerability of medicines used in paediatrics and the availability of medicines studied in paediatric populations.

The 10-years Report from the Paediatric Committee and European Medicines agency about the application of the Paediatric Regulation shows a very positive impact on paediatric drug development, namely [3]: more medicines for children as well as more and better information for prescribers and patients, better paediatric research and development, more regulatory support for paediatric matters and the integration of paediatrics as integral part of medicines development. Comparing the number of centrally authorized medicines for children in 2004-2006 and 2012-2014, it was observed an increasing number of new paediatric products (from 19 to 30) and new

paediatric indications (from 12 to 38). Moreover, the number of new medicines and new pharmaceutical forms adequate for children approved from 2007 until 2015 were 238 and 39 respectively [3].

However, the impact of the Paediatric regulation on the development of paediatric formulations with the off-patent medicinal products that have been used during years as unlicensed or off-label in the paediatric population was not so positive, being the first PUMA authorized in 2011 and the second in 2014 [3]. Maybe that explains why the governmental initiatives and these regulation implemented in Europe to encourage drug research in children have had a marginal impact on unlicensed and off-label drug use rates on inpatient and outpatient health care settings [4,5].

Use of unlicensed and off-label Extemporaneous preparations in paediatric population

Many medicines already available on the market for adults continue to be used on children without appropriate studies in paediatric population and the use of unlicensed and off-label medicines in children is still a reality [4-10].

In addition to the lack of knowledge of adequate dosages that may lead to serious adverse reactions, other problems arise associated with the use of adult dosage forms in children, namely: use of magistral and officinal preparations without information about stability, administration of excipients included in the drug adult formulation could be harmful to the paediatric population [2,5,11]. In general excipients are considered to be “inert”, however in children and particularly in neonates some of them have demonstrated some activity and are potentially toxic for this population with increasing reports of adverse reactions [12]. There are few studies that analyse that and discuss the excipients included in the different trade market and generic medicines available in the market with the same active substance. In a pilot study that analysed 790 adult medicines [13], it was observed that all of them contained one or more excipients listed on the Guideline Excipients in the label and package leaflet of medicinal products for human use [14]. When children take extemporaneous preparations there is a risk of exposure to harmful doses of these excipients leading to toxicity.

Although there is lack of studies on the quality and stability of extemporaneous preparations, some authors have developed stability studies with simple formulations for some drugs frequently administered off-label and unlicensed, such as sildenafil [15,16], metformin [17], clonidine [18], propafenone [19]. Moreover the bioavailability of extemporaneous preparations is not studied, however it is well known that the bioavailability of the drug is modified when a dosage form is extemporaneously compounded [11,20].

The challenge of developing adequate formulations for children

The development of age-appropriate and acceptable paediatric dosage forms is a complex and challenging process, as it is necessary to have in consideration children’s acceptability and preferences for different formulations and to understand the physical and biochemistry differences between children and adults [21]. Acceptability of medicines in children and caregivers have an important impact on therapeutic adherence and consequently on the safety and efficacy [22,23]. The acceptability depends on the end-user and on the pharmaceutical characteristics, the first one is not a modifiable factor but the second one is. Some of these characteristics that could influence the acceptability of a medicine and that should be a critical point during the design of a new dosage form are: palatability and swallowability (e.g. size, shape, texture), appearance (e.g. color, shape, embossing), complexity of administration, the required dose (e.g. volume, number of tablets or capsules), dosing frequency and duration of treatment, the administration device, the containers closure system, the mode of administration and any related pain or discomfort [23].

Design of oral dosage forms for children should consider differences from adults like swallowing abilities, taste preferences and dosage requirements [24]. For years, liquid formulations were preferred for children as they allow to adjust doses across age groups. However, new oral formulations have been considered and recommended for children, namely orodispersible tablets and tablets used to prepare oral liquid preparations suitable for younger children, granules, multi-particle dosage forms, mini-tablets and pellets [24,25]. Examples of innovative oral dosage forms are oral lyophilisates, orally disintegrating mini-tablets, orally disintegrating films and more recently was developed a “pill swallowing cup” (the appropriate dose of drug is inside of the cup, which is filled with a liquid and then the patient drinks it) [24].

In addition, another critical point during the development of paediatric formulations is the selection of the excipients to be included, once excipients are often not “inert” from a biopharmaceutical perspective [24]. In this way, and following the Guideline on pharmaceutical development of medicines for paediatric use [23] when selecting an appropriate excipient for inclusion in a paediatric medicinal product some aspects should be considered: (i) the function of the excipient in the formulation and potential alternatives, (ii) the safety profile of the excipients for children in the target age group(s) on the basis of single and daily exposure, (iii) the expected duration of the treatment, (iv) the severity of the condition to be treated, (v) the patient acceptability including palatability and, (vi) allergies and sensitization.

As mentioned above, acceptability depends also on the characteristics of the end-user and some parameters like capability, acute or long-term illness, caregiver convenience, disabilities and cultural differences. Therefore, formulations that are more attractive to targeted children must be explored.

FINAL REMARKS

It is well known that the paediatric use of off-label and unlicensed medicines are a reality and that there is a lack of medicines well studied for children. Although there are already some studies focusing on the perceptions of children [26-28], it is still important to improve our knowledge in this area. It is fundamental to develop research in order to understand attitudes and preferences of children and their caregivers with the aim of developing dosage forms and formulations which are children-friendly.

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