Formulation of Drug Product for Paediatric Population – Challenges

Designing the adequate drug product for the paediatric population is a huge challenge and is the most important way to ensure patient adherence to treatment. Such a development should be patient-centred, considering the specificities of the end-user population.

One of the main specificities of the paediatric population is that this is a heterogeneous population; potential paediatric patients are neonates, newborns, infants and toddlers, young children (preschool and school children), and adolescents. Therefore, it represents a wide age range from 0 to 16/18 Years[1]. In addition, childhood is a period of maturation of the human body, so physiology is different from that of the adult population and between sub-paediatric populations. This fact induces differences and evolution in pharmacokinetics and pharmacodynamics of drugs all along childhood, until adulthood. Therefore, paediatrics formulations must allow administration of an accurate and defined dose to patients of widely varying weight and age[2].

On top of that, children's ability to manage different dosage forms/devices will also evolve during childhood; the oral route is the preferred one for long-term administration, whereas the intravenous route is the one for acute illness. Liquid drug products are usually recommended for infants and younger children. The age at which a child is able to swallow conventional tablets is of great importance for his safety; it is considered that a child is able to safely swallow a solid oral dosage form at about six years old[3]. Therefore, a large panel of pharmaceutical dosage forms can be envisaged by formulation scientists, with their own hurdles, but also hurdles specific to the paediatric population.

The regulatory landscape and requirements, the main formulation solutions, and their principal respective challenges are presented below.

In 1997, USFDA was the first authority to assess the need of a regulatory frame on pharmaceutical development of safe and effective paediatric medicines. In 2012, the FDA Safety and Innovation Act definitely acts on the Best Pharmaceutical for Children Act (BPCA, 2002, voluntary with incentives) and on the Pediatric Research Equity Act (PREA, 2003, mandatory)[4].

In Europe, discussions about the need of such a regulation started only in 1997, and the Paediatric Regulation came into force in the European Union (EU) on 26 January 2007[4]. According to Article 15, marketing-authorisation applicants are required to include in their paediatric investigation plan (PIP) any measures to adapt the formulation of the medicinal product to be age-appropriate in different subsets of the paediatric populations.

The International Conference of Harmonization (ICH) released in 2000 the ICH Harmonized Tripartite Guideline "Clinical investigation on medicinal products in the pediatric population" E11 to encourage the development of paediatric medicines[4].

In December 2007, the World Health Organisation (WHO) launched its initiative "Make medicines child size" in order to raise awareness and accelerate action to meet the need for improved availability and access to child-specific medicines. The WHO Model Formulary for children, 2010, provides independent prescriber information on dosage and treatment guidance for medicines based on the WHO Model List of essential medicines for children, first developed in 2007 and reviewed and updated every two years[1]. In Annex 5 of WHO Technical Report Series No. 970, 2012, WHO presents a "Points to consider" document on the formulation of paediatric medicines. The objective is to inform regulatory authorities and manufacturers on issues that require special attention in pharmaceutical formulation.

The regulatory landscape has thus deeply changed during recent years, mainly to encourage firms to develop medicines adapted to children. However, things have to continue to evolve to have most drug products custom-made for this population, and the same process has to be followed for the geriatric population. For instance, it is still difficult for sponsors to put in place clinical studies in paediatric populations because it requires obtaining data on adults first, with adult formulation. Such a process delays the possibility of access for children to adapted medicines. Thus, formulations suitable for children should be considered and explored early in the development of a drug[5].

Regarding pharmaceutical development of paediatric medicines, route of administration and dosage form, dosing frequency, container closure system, measuring / administration device and packaging, as well as minimum age of the patients (and thus relevant developmental physiology) have to be determined. Therefore, many factors have to be taken into account: the age characteristics of the children in the target group(s), the disease

to be treated (and the condition-related characteristics of the child), the criticality of the dose and the dosing regimen, the age-associated activities of the target children, the maximum duration of the therapy and the dosing frequency, the environment setting where the product is likely to be used, the child's and caregiver's characteristics and their behaviour are of utmost importance[6]. The EMA Reflection Paper: Formulations of choice for the paediatric population (EMEA/CHMP/PEG/194810/2005 is a very interesting document to choose the most appropriate route of administration and dosage form, as it reviews the different types of oral dosage forms available for paediatric use and focuses on key factors to improve their acceptability for the paediatric population[7].

The choice of the route of administration and the dosage form will strongly impact on the choice of the excipients. Since oral administration is the preferred route and since many drugs are not soluble in water and have a bitter or unpleasant taste, excipients include in particular solubility enhancer agents, sweetening agents, taste-masking agents, colouring agents, and antimicrobial preservatives. The choice of excipients is the main point addressed by regulatory requirements from a formulation point of view. According to EMA/CHMP/QWP/805880/2012 rev. 2 Guideline on pharmaceutical development of medicines for paediatric use, the choice of suitable excipients in such medicinal products is one of the key elements of the development. The inclusion of any excipient requires special safety considerations as the intake of an excipient may result in a different exposure in children than in adults, or in children of different ages, as it may have different effects on developing organs. Therefore, some aspects have to be considered when selecting an excipient for the formulation of paediatric drug product: function of the excipient in the formulation and potential alternatives; safety profile of the excipient for children; expected duration of the treatment; severity of the disease to treat and the therapeutic alternative; patient acceptability; allergies and sensitisation[6].

According to Annex 5 of WHO Technical Report Series No. 970, 2012, WHO "Points to consider" document, the challenge for paediatric medicines compared to adult ones is that excipients may lead to adverse reactions in children that are not met in the adult population, or are not seen to the same extent. Moreover, in the development of paediatric medicines, the number of excipients and their quantity in a formulation should be the minimum required to ensure an appropriate product with respect to performance, stability, palatability, microbial control, dose uniformity and other considerations to support product quality[1].

For instance, for products intended to be marketed in the USA, only excipients considered as GRAS (Generally Recognized As Safe), already used in human medicinal products and

included in the FDA Inactive Ingredient Database can be used in formulation[8].

Dosage forms adapted to the paediatric population are oral solid preparations such as powder, granules, tablets (including effervescent, soluble, dispersible, orodispersible, chewable tablets) and mini-tablets (i.e. less than 4mm diameter[1]); capsules; oral liquid preparations (solutions, suspensions, drops, syrups); oromucosal, nasal, cutaneous and transdermal preparations; nasal preparations; preparations for inhalation; eye and ear preparations; rectal preparations (suppositories and liquid rectal preparations); preparations for parenteral administration. All these preparations can be immediate release forms, but some of them can also be modified release (MR) preparations. Such MR forms can be used to reduce dosing frequency and so improve compliance. Fixed dose combinations, namely medicine combining several drugs, are also interesting to simplify therapy and improve patient adherence, especially for chronic diseases that require several drugs.

For each development, patient acceptability has to be anticipated, mainly based on product palatability, including adequacy of the taste according to country of marketing (using e-tongue or test panel), appearance and dosing volume; administration mode and device are also taken into account. Administration by mixing with food, drinks or other vehicles has also to be envisaged and appropriate studies put in place to assess the compatibility

and the stability of the product with the vehicles. Use of measuring/ administration devices has also to be evaluated to assess of the accuracy of the actual administrated dosage, which can be critical in both terms of safety and efficacy for drugs with a narrow therapeutic window.

To allow high dose flexibility without increasing costs for industrials, as well to deliver a single dose form which participates in avoiding accidental dosing errors, Synerlab Développement, a CDMO based in Orléans (France) with a successful track-record on liquid and solid oral dosage forms, recommends, but does not limit, using dispersible or orodispersible tablets; powder in sachet or capsules; multi-particulate dosage forms like granulates, pellets or mini-tablets in sachets or capsules. A multi-particulate dosage form consists of a multiplicity of small discrete units with some desired characteristics[3].

The main challenge when developing dispersible or orodispersible tablets is the taste of the dosage form, mainly led by the taste of the API. This is a real main challenge as children have a well-developed sensory system; they are able to recognise sweetness and saltiness from an early stage. Such an issue can be solved using sweeteners and / or taste-masking and / or flavouring agents that will have to be safe and non-cariogenic[1]. Another option is to use taste-masked coated pellets or granules in the tablets formulation[3], but the formulation and manufacturing parameters have to be carefully defined to avoid the crushing of particles during the tabletting step and thus breaking the taste-masking coating. The sensation in the mouth for orodispersible tablets and required liquid volume for dispersible tablets can also be hurdles.

The formulation of powders, granules, and pellets in sachet will also be led by drug product taste, as at least a liquid or semi-solid food has to be used for administration. Regarding capsules, they are intended to be taken intact, even if maximum acceptable capsule size is not well known[6], or they can be opened and emptied to be used with an administration vehicle; specific capsules, such as the Sprinkle Capsule from Capsugel / Lonza, are designed for such an application to facilitate their opening. In this case, taste is again a

challenge, but other considerations are to be taken into account such as the impact of the content on capsules opening. Mini-tablets can also be considered as difficult to swallow, even when administrated with a semi-solid vehicle, so dispersible mini-tablets can be an interesting alternative in this case. Lastly, some of multi-particle form, i.e. granulates, pellets and mini-tablets, can be used for both immediate and/or modified release.

Concerning oral liquid preparations, the formulation can be tricky since on the one hand taste is a challenge and on the other hand higher restrictions regarding the use of solvents occur for this population (e.g. alcohols), whereas many drugs are not soluble in water. In addition, as they are multiple dosage forms, it is necessary to well-define and assess an adequate dosing device to avoid any mistake that could result in a lack of efficacy and / or a safety risk. However, this dosing device could still be helpful as it often allows dosing according to body weight. The counterpart is that these formulations tend to be less stable over time, especially after opening.

Developing adequate paediatric medicines is thus a huge challenge. Each detail of the product, including choice of the dosage form and of the excipients, and its associated device has actually to be well-designed and assessed in the regulatory dossier. Moreover, depending of the age of the target population, it can be necessary to adapt the dosage form. Therefore, as children are not "small adults" from a physiological point of view, it is absolutely necessary to develop medicines adapted to this specific population(s), which is why Synerlab Développement works in this way, keeping aware of regulation changes and searching for new solutions.

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