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Patient acceptability, safety and access: A balancing act for selecting age-appropriate oral dosage forms for paediatric and geriatric populations

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ABSTRACT

The selection and design of age-appropriate formulations intended for use in paediatric and geriatric patients are dependent on multiple factors affecting patient acceptability, safety and access. The development of an economic and effective product relies on a balanced consideration of the risks and benefits of these factors. This review provides a comprehensive and up-to-date analysis of oral dosage forms considering key aspects of formulation design including dosage considerations, ease of use, tolerability and safety, manufacturing complexity, stability, supply and cost. Patient acceptability has been examined utilising an evidence-based approach to evaluate regulatory guidance and literature. Safety considerations including excipients and potential risk of administration errors of the different dosage forms are also discussed, together with possible manufacturing and supply challenges. Age appropriate drug product design should consider and compare i) acceptability ii) safety and iii) access, although it is important to recognise that these factors must be balanced against each other, and in some situations a compromise may need to be reached when selecting an age-appropriate formulation.

1. Introduction

Patient centric pharmaceutical drug product design may be described as "the process of identifying the comprehensive needs of individuals or the target patient population and utilizing the identified needs to design pharmaceutical drug products that provide the best overall benefit to risk profile for that target population over the intended duration of treatment" (Stegemann et al., 2016). The selection and design of patient-centred oral pharmaceutical dosage forms continues to be one of the most significant challenges in the development of medicinal products for paediatric and geriatric populations due to the diverse needs and characteristics of these patient groups. In recent reviews, various patient related factors have been described (Drumond et al., 2017; Ivanovska et al., 2014; Liu et al., 2014; van Riet-Nales et al., 2016b; Zajicek et al., 2013), although most have been in relation to the development of formulations for use in children. It is well acknowledged that a broad range of unique issues need to be taken into consideration in these two heterogeneous populations, some of which may not be seen to the same extent, if at all, in adults. For example, a frequently encountered issue includes determining the suitability of tablet and capsules sizes in relation to patients' age and ability to swallow solid oral dosage forms (Ranmal and Tuleu, 2013). Age-related physiological changes and vast differences in required dose also present particular challenges. There is still very limited evidence based data which can be used to provide specific recommendations. The availability of regulatory guidance on the pharmaceutical development of paediatric medicines is welcomed (EMA, 2012a), although detailed rationale for the recommendations is not provided. Similar guidance on medicines for geriatric patients has not yet been published,

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although a number of activities are on-going including the development of a reflection paper (EMA, 2013; van Riet-Nales et al., 2016a).

The International Conference on Harmonisation (ICH) pharmaceutical development guideline (Q8 (R2)) states "in all cases, the product should be designed to meet patients' needs and the intended product performance" (ICH, 2009). Therefore when defining the Quality Target Product Profile (QTPP) and selecting an appropriate dosage form, it is important to consider patient requirements and how the product may be taken alongside the complex technical challenges and feasibility of pharmaceutical development and manufacturing processes. In addition, the relative cost and supply of the product are important considerations to ensure global availability.

The criteria for the selection of an age-appropriate dosage form have previously been identified as being efficacy/ease of use, safety and patient access (Sam et al., 2012). The aim of this review is to provide a comparison of different oral dosage forms according to these three criteria in order to assist pharmaceutical product formulators to select and develop the most suitable product for paediatric and geriatric patients. For the purposes of this review, it is assumed that formulators will have already considered active pharmaceutical ingredient (API) properties and other preformulation considerations, hence this topic will not be included. Disease to be treated would have an impact on the development of pharmaceutical products for children and older adults; however, a disease-specific evaluation for developing age-appropriate formulations would render an entirely new angle of review. The anticipated duration of treatment (short term versus long term) and severity of the condition are also considerations when assessing the benefit risk balance of a formulation and the excipients to be used (EMA, 2012a).

2. Factors to consider for paediatric/geriatric oral dosage form design

Choice of formulation may be affected by the properties of the API, target age group and disease to be treated (Wang, 2015), as well as culture and geographical location. In designing a drug product intended for use in paediatrics or older adults, all typical considerations of adult dosage form development apply. As for any drug product, API properties which can impact the selection of dosage form include for example biopharmaceutical classification, physico-chemical properties, stability, dose and required release rate (Kuentz et al., 2016). For instance, APIs with high solubility (BCS I and III) are generally more suitable for oral solutions and syrups compared to poorly soluble APIs, and mini tablets and oral films may not be appropriate for APIs which require high doses due to limitations in drug loading per unit dosage form. Furthermore, API properties may influence the manufacturing method and processing route that may be applied to a particular dosage form (Leane et al., 2015). The taste of an API should also be considered when selecting an oral dosage form, and approaches to minimise the interaction of an aversive-tasting API with taste receptors in the mouth should be utilised. Formulations for paediatrics and older patients add complexity to the development process due to the diverse nature of the patient population, safety and compliance considerations. Hence, additional factors need to be taken into account when developing products for these groups.

As stated above (Section 1), Sam et al. (2012) previously proposed a structured framework for assessing and balancing the benefits and risks of different pharmaceutical dosage forms for paediatric use in relation to 3 key criteria; efficacy/ease of use, safety and patient access (Sam et al., 2012). The ease of use of a medicinal product (including dose flexibility), is one aspect that affects its overall acceptability to patients, and in this review, this broader concept of patient acceptability has been considered instead. The factors to consider in relation to these 3 criteria are outlined in Table 1. Patient acceptability is determined by the characteristics of the product and the user and may be defined as "an overall ability of the patient or caregiver (defined as 'user') to use a medicinal product as intended (or authorised)" (EMA, 2012a; Kozarewicz, 2014). It can have a significant impact on patient adherence and therefore safe and effective therapy, and should be considered for all patients, including older adults. A pharmaceutical product must have acceptable safety and a positive benefit risk profile and the safety profile of a formulation may differ according to the age of the patient. To enable patient access to the drug product, manufacturability, stability, supply chain and cost need to be considered. Key features of oral dosage forms with respect to their patient acceptability, safety and access, based on pharmaceutical development guidelines, the reflected literature and the authors' experience, are summarised in Table 2 and discussed in greater detail in the following sections.

3. Acceptability

Oral dosage forms may be divided into those which provide flexible doses, such as liquids and multiparticulates, and those which provide unit doses, such as tablets and capsules. Each have

Table 1
Factors to consider for the selection of an oral dosage form.

Patient Acceptability	
Dosage considerations	The ability of the formulation to be sub-divided without impact on the product's safety and efficacy to allow flexible and optimal dosing to the patient
Dose preparation	The requirement for any manipulation or measurement of a quantity of the formulation prior to administration.
Ease of ingestion	The ease with which the product may be taken by the patient, including aspects such as palatability, swallowability, size and quantity of solid dosage units, volume of liquid.
Safety	
Acceptable tolerability and safety	The product should not give rise to an unacceptably high risk of adverse effects, acute toxicity, organ toxicity or GI side effects, which are not directly caused by the API.
Risk of mis-dosing	The risk of administration of an incorrect dose, for example by incorrect handling, incorrect measurement and/or incorrect administration of the required dose.
Access	
Stability	The shelf-life of the product, including in-use if appropriate.
Manufacturing and development complexity	How complicated the required development process and manufacturing and packaging operations are, including the need to use specialised, non-routine processes.
Supply chain	How the product is stored and transported, including in resource-poor settings.
Relative cost	The estimated magnitude of cost of a dosage form compared to the other dosage forms, excluding API cost.

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