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Regulatory perspectives on acceptability testing of dosage forms in children

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ABSTRACT

Current knowledge about the age-appropriateness of different dosage forms is still fragmented or limited. Applicants are asked to demonstrate that the target age group(s) can manage the dosage form or propose an alternative strategy. However, questions remain about how far the applicant must go and what percentage of patients must find the strategy 'acceptable'.
The aim of this overview is to provide an update on current thinking and understanding of the problem, and discuss issues relating to the acceptability testing. This overview should be considered as means to start a wider discussion which hopefully will result in a harmonised, globally acceptable approach for confirmation of the acceptability in the future.

1. Discussion

Development of age-appropriate dosage forms is critical for assuring adequate patient adherence to the treatment and guaranteeing safe and effective therapy. The concept of age-appropriateness must not be limited to the development of dosage forms commonly considered appropriate for use in children. Confirmation of the acceptability is an important aspect in the pharmaceutical development and it constitutes essential part of a state-of-the-art development program. Development of a medicine can only be concluded when it is demonstrated that the medicine will be administered (by a child and/or caregiver) and taken (by a patient – child) as intended.

Acceptability is an overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorised). Acceptability of a medicinal product is likely to have a significant impact on the patient's adherence and consequently is likely to have an impact on safety and efficacy of the product. As a general rule, acceptability aspects should be embedded in the development program and evaluated, (preferably) during the clinical study (preferably) with patients from target age group(s).

Acceptability is driven by the characteristics of the user (age, ability, disease type and state) and by the characteristics of a medicinal product such as:

- Palatability.
- Swallowability (size and shape, integrity of dosage form, e.g. film-coating).
- Appearance (e.g. colour, shape, embossing, etc.).
- Complexity of modification prior to administration (if required).
- Required dose (e.g. the dosing volume, number of tablets, break marks, etc.).
- Required dosing frequency and duration of treatment.
- Selected administration device (if any).
- Primary and secondary container closure system.
- Actual mode of administration.

Palatability is one of the main (but not exclusive) elements which affect patient's acceptability of an oral medicinal product. It is defined as the overall appreciation of a (often oral) medicine by organoleptic properties such as vision (appearance), smell, taste, aftertaste and mouth feel (e.g. texture, cooling, heating, trigeminal response), and possibly also sound (auditory clues). It is determined by the characteristics of the components (active substance and excipients) and the way the active substance is formulated into a medicine. Palatability is also relevant for other routes of administration e.g. buccal, nasal, inhalation use, and whenever

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Table 1
Critical attributes to be included in acceptability testing.

Critical attributes to be included in acceptability testing	
Oral use	
Monolithic solid dosage forms to be swallowed	Primary aspects Size and shape; taste and aftertaste for uncoated dosage forms. Secondary aspects Visual aspects (embossing, surface aspects, colour); need for training or dosing aids and devices.
Multiparticulate solid dosage forms to be swallowed	Primary aspects Particle size, shape, texture (surface aspects) and hardness (grittiness); taste and aftertaste for uncoated multiparticulate; dose volume (quantity of multiparticulate that needs to be taken); need for a measuring/counting device and ease of administration. Secondary aspects Not identified.
Solid dosage forms to be chewed	Primary aspects Taste and aftertaste and the mouth feel; smell; time needed to chew and effort required to chew (duration of administration). Secondary aspects Visual aspects (embossing, surface aspects, colour).
Solid dosage forms to be dispersed (solubilised) in the mouth (e.g. tablets, lozenges, etc.)	Primary aspects Taste and aftertaste and the mouth feel; smell; time needed to dissolve/disperse (duration of administration). Secondary aspects Visual aspects (embossing, surface aspects, colour).
Liquid dosage forms – solution, suspension	Primary aspects Taste and aftertaste; smell; volume, viscosity and the mouth feel; need for a measuring device and ease of preparation/administration; visual aspects (overall appearance). Secondary aspects Size of the primary packaging (oversized bottle may be difficult to carry).
Buccal and sublingual use	
Solid and semi-solid	Primary aspects Size; taste and aftertaste; mouth feel and local tolerance (potential for irritation); smell; time needed to be kept in the mouth and ease of to remain in place for the dosage form (duration of administration); site of application and ease of administration (but in addition to the user instructions). Secondary aspects Visual aspects (embossing, surface aspects, colour).
Liquid	Primary aspects Volume; taste and aftertaste; mouth feel and local tolerance (potential for irritation); smell; time needed to be kept in the mouth (duration of administration). Secondary aspects Visual aspects (appearance, colour).
Parenteral use	
Intravenous preparations	Primary aspects Injection volume; pain (discomfort) associated with composition (pH, osmolarity, excipients, etc.), needle size, needles vs catheters, rate of administration, administration duration, method of administration (bolus/push injection). Secondary aspects Visual aspects (appearance, colour of solution); method of preparation including need for dilution and flushing; ease of dosing (measuring correct dose, etc.).
Subcutaneous preparations	Primary aspects Injection volume; pain (discomfort) associated with composition (pH, osmolarity, excipients, viscosity, etc.), needle size, site of injection; administration device (prefilled syringes, pen) and ease if handling before administration (clear instructions). Secondary aspects Visual aspects (appearance, colour of solution); method of preparation including need for dilution; ease of dosing (measuring correct dose etc.).
Intramuscular preparations	Primary aspects Injection volume; pain (discomfort) associated with composition (pH, osmolarity, excipients, viscosity, etc.), needle size, site of injection; administration device (prefilled syringes, pen) and ease if handling before administration (clear instructions). Secondary aspects Visual aspects (appearance, colour of solution); method of preparation including need for dilution; ease of dosing (measuring correct dose etc.).
Dermal/cutaneous (topical) use	
	Primary aspects Texture (greasy, sticky, etc.); smell; area of application; local tolerance (irritation, sensitisation, pain, etc.) and feeling after application (e.g. cooling, burning, residue on the skin, etc.); visual aspects (appearance, colour, etc.); application aspects: quantity to be applied, ease of application (e.g. need for occlusion or dressing, need rubbing, need to clean the area of application etc.), interference with daily routine (e.g. area of the application not to be washed, etc.). Secondary aspects Lack of device and the way of administration.
Transdermal use (patches)	
	Primary aspects Area of application; local tolerance (irritation, sensitisation, pain, etc.); visual aspects (appearance, colour, etc.); application aspects: size of the patch, interference with daily routine (balance between staying in place