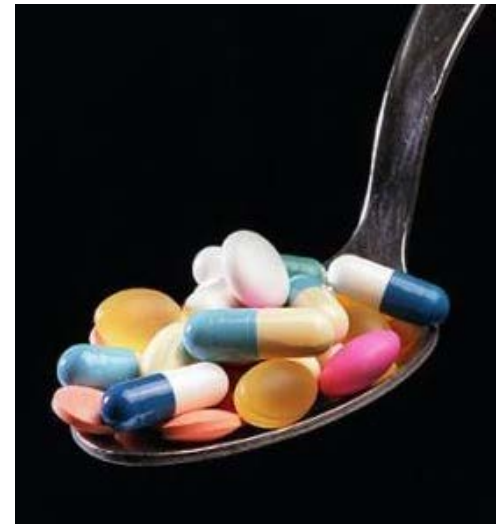


Patient Acceptability

EMA Regulatory Considerations

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Guidelines covering acceptability

Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev. 2

- In effect since 15.2.2014
- Scope

“The principles of this guideline should be considered during the pharmaceutical development of all paediatric medicines as proposed in marketing-authorisation applications (MAAs) or applications to extend or vary marketing authorisations to the paediatric population (MAVs). Depending on the phase of the development, the principles of this guideline should also be considered for the purpose of the paediatric investigation plan (PIP) applications. “

Reflection paper: Formulations of choice for the paediatric population
EMA/CHMP/PEG/194810/2005

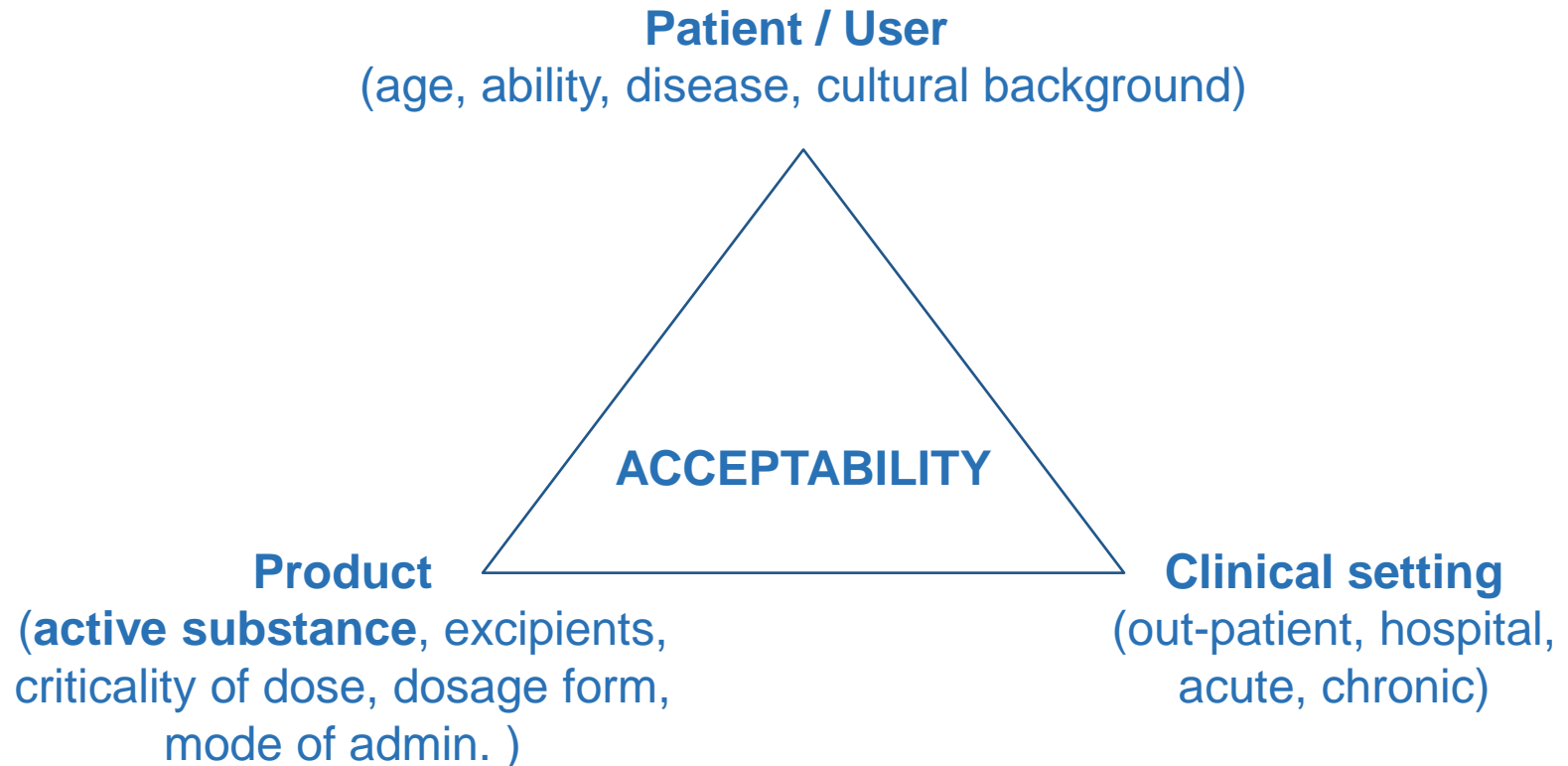
Guidance on acceptability

- High level guidance
 - Rational and points to consider
 - Risk-benefit considerations
 - Justification of used approach by applicant
- **Section 10. Patient acceptability**
- Additional points on acceptability aspects found across guideline e.g. under dosage form considerations

“Acceptability of and preference among the different paediatric dosage form(s) is known to vary between children. The child’s age, individual health status, behaviour, disabilities, background and culture are currently considered as the most likely parameters determining the child’s acceptability and preference.”

Patient / User acceptability

Overall ability and willingness of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorised).



Components of acceptability

- Palatability (taste, after-taste, mouth-feel, fragrance, appearance)
- Swallowability (size and shape, integrity of dosage form, e.g. film-coating; volume)
- Appearance (e.g. colour, shape, embossing, etc.)
- Required dose (e.g. the dosing volume, number of tablets, break marks, precision of dose etc.)
- Complexity of modification prior to administration (if required)
- Required dosing frequency and duration of treatment
- Selected administration device (if any)
- Primary and secondary container closure system
- Actual mode of administration (ease, practicality, pain or discomfort)

Oral Dosage forms – acceptability (1)

- Swallowability and palatability fundamental components
- Oral liquids
 - In principle for all ages
 - functional intestine (enteral feeding possible)
 - appropriate for condition to be treated
- volume vs. palatability
 - *“Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted preparation allows for better taste masking.”*
- Volume vs. ease of administration vs. necessary dosing precision
- Measuring device
 - Ease of use vs. precision needed
- Dispersible and effervescent tablets – as liquids

Oral Dosage forms – acceptability (2)

- Powders and granules
 - Quantity or volume, solid or dispersed (in liquid or soft food)
 - Particle size
 - As liquid from birth
 - Volume and palatability
 - As solid from around 6 months
 - with semi-solid food (compatibility/food-effect!)
- Tablets (taken intact)
 - size, shape and number of tablets
 - *“The size and shape of a tablet are fundamental to the ability of a child to swallow it. Therefore, the acceptability of the size and shape of tablets by the target age group(s) should be justified, and where relevant supported by appropriate studies or clinical evidence.”*

Oral Dosage forms – acceptability (3)

- Concept of ‘mini-tablets’

“Small tablets containing a fraction of the required dose may be considered as a measure to improve both the acceptability and/or dosing flexibility of tablets. Such small tablets are designed so that the dose for children in the different target age group(s) is achieved by the intake of one or several small tablets (concept sometimes referred to as “mini-tablets”).

If a dose requires several tablets to be taken to achieve one dose, the acceptability of the required number of tablets should be discussed and justified for the relevant target age group(s).”

- Orodispersible and chewable tablets/granules
 - Volume and palatability!
- Capsules
 - Size when taken intact
 - *“Where appropriately justified, hard capsules may also be opened and their contents taken as such, provided that the feasibility of opening the capsule and removing the contents from the capsule has been demonstrated.”*

Assessment of acceptability

- Integral part of development
 - New products irrespective of PIP status
 - Products with post-authorisation changes (e.g. variations in composition or tablet size)
- Preferably studied in children themselves as part of a clinical study involving the proposed medicinal product
- **Methodology not specified**
 - Justification of age- (and product-) appropriateness of methodology
 - Justification of criteria in view of user and product perspective
 - **Overall benefit-risk considerations** for (lack of) acceptability, implications for (non-)compliance

Palatability

- Oral, oromucosal, nasal or inhaled products
- Taste, after-taste, fragrance, and/or mouthfeel / texture
- Composite of active substance, excipients and dosage form
- Neutral or specific flavour – but not 'candy like'
- Taste masking/palatability strategy to be justified
- Assessment of palatability
 - Recognition of taste issues early in drug development !
 - Palatability testing of AS and formulations
 - Taste sensors
 - Trained adult panels
 - Healthy paediatric volunteers (limited scope)
 - In paediatric clinical trials
 - Confirmation of palatability as part of acceptability assessment in CT

Alternative strategies to administration of solid oral dosage forms

*“When oral solid preparations are to be given to children, it is likely that **some** children may not be able or willing to take the dosage form as intended, even when the dosage form is generally considered as age appropriate.*

In the absence of alternative age appropriate dosage forms, other strategies for administering the oral solid preparations should be considered by applicants and discussed (e.g. dispersing or crushing tablets, opening of capsules, mixing with food or drinks). In addition to the agreed age-appropriate preparation, applicants are encouraged to propose alternative strategies for administration of the preparation.

*If an alternative strategy is proposed the applicant, then the **approach should be verified** and instructions on the modification(s) to be conducted should be given in the SmPC and PIL.”*

- **Not an excuse for poor development**

Poor / less than optimal acceptability

- New dosage form / formulation or route of administration?
- Alternative methods of administration?
- **Where to draw the line?**
- *“Adequate patient acceptability is **not to be understood as 100% acceptability** of a medicine by children in the target age group(s).”*
- *“However, the suitability of the chosen method to test the patient acceptability and the **appropriateness of the applied limits** should be discussed and justified in terms of **benefit-risk considerations, including risks at population level** (e.g. emergence of microbiological resistance due to poor acceptability of different preparations with antibiotics).*
- *The characteristics of the target age group(s), the condition relevant to the paediatric medicine, single or multiple use, the duration of treatment and any co-medication should also be considered. “*

Risks considerations

- “The attractiveness of paediatric medicinal products should be carefully balanced between the risk of inadequate patient acceptability and accidental intake, and should be discussed with regards to all aspects of the medicine, i.e. the dosage form, the formulation, the strength and the primary and any secondary packaging. “
 - Choking and/or aspiration
 - Loss of dosage form functionality (e.g. chewing, crushing)
 - Loss of part of the dose; under- or overdosing;
 - Local tolerance issues/toxicities/pain
 - Implications of poor acceptability and compliance (disease type and severity)

Considerations of risk - examples

Swallowability of solid dosage forms – intact or chewing allowed

- Coated solid dosage forms
 - Loss of taste masking → palatability → acceptability issue
 - Loss of prolonged release/dose dumping → high plasma peak → side effects / toxicity
 - Loss of gastroresistance → reduced absorption (acid sensitive, targeted intestinal absorption) → loss of efficacy

User friendliness - risk for dosing errors

- 'Criticality' of dose vs practicality and ease of dosing
 - Precision of volume vs measuring device
 - Number of (mini-)tablets
 - counting , sachet or device
 - Volume of vial vs smallest dose (10x error)
 - Complicated administration (dilutions, NG tube)

Paediatric Investigation Plans

- Key binding elements addressing acceptability related issues
 - **Clinical trials**
 - Assessment of acceptability (and palatability) - 2nd endpoint
 - Effects of co-administration with food (case-dependent)
 - Recording of co-administered food items; predefined food items and amount; comparative BA study in adults;
 - **Quality measure**
 - Assessment of acceptability (and palatability) (in CT)
 - Smaller / lower strength tablet(s)
 - Data supporting alternative administration approach
 - Compatibility (chemical/physical) with any proposed food items
 - Feasibility of dosing through NG tube (compatibility/dose recovery)
 - More concentrated solution for s.c. administration
 - CT: availability at initiation of e.g. NG dosing data; clear instructions for dilution and/or administration

Problem statement – steps forward

- More data emerging in public domain since writing of guideline
- Data emerging from PIPs (and more to come)
 - Still fragmented
 - Insufficient for setting of detailed requirements in guidelines
 - Problematic both for regulators and industry
- Collaboration between regulators, academia and industry needed
 - Recognition of current knowledge and gaps
 - Recognition of points of agreement and disagreement
 - Conclusion of (some) steps to bridge gaps

High hopes for the current workshop!