EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 3 January 2013
2 EMA/CHMP/QWP/805880/2012 Rev. 1
3 Committee for Medicinal Products for Human Use (CHMP)
4 Paediatric Committee (PDCO)

5 Guideline on pharmaceutical development of medicines 6 for paediatric use

7 Draft

Draft Agreed by QWP	**February 2011**
Draft agreed by SWP	March 2011
Draft agreed by PDCO	April 2011
Adoption by CHMP for release for consultation	May 2011
End of consultation (deadline for comments)	31 December 2011
Revised version agreed by QWP for release for second consultation	September 2012
Revised version agreed by PDCO for release for second consultation	November 2012
Revised version adopted by CHMP for release for second consultation	November 2012
End of second consultation (deadline for comments)	31 March 2013

8

Comments should be provided using this template. The completed comments form should be sent to qwp@ema.europa.eu

9

Keywords *child, pharmaceutical development, quality*

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Note:

The draft guideline on Pharmaceutical Development of Medicines for Paediatric Use (Doc. Ref.: EMA/CHMP/QWP/180157/2011) was released for public consultation in 2011. Following consultation the guideline was revised to address comments received. Given that important revisions have been made, this revised version of the draft guideline is now published for a second public consultation.

CHMP would like to bring to your attention the points below which are opened for the second consultation:

1. Section 6.2.1 *Handling of oral solid preparations to facilitate administration*

Additional paragraph under section 6.2 has been proposed to address handling of oral solid preparations which is done to facilitate administration. This section combines and expands on initially proposed sections on *Sub-division of tablets* and *Crushing tablets.*

2. Section 10 *Mixing with food*

Mixing with food and drinks may be an important approach for assuring or improving patient's acceptability, or to facilitate administration of medicines to children. Therefore additional section dedicated to this aspect has been included in the revised Guideline.

3. Patients acceptability

Assurance of patients' acceptability through out the life cycle of a medicinal product plays an important role in treatment compliance. This section of the guideline highlights the need to consider additional studies when changes to the formulation (re-formulation of the product) are proposed and it is apparent that such changes may affect acceptability, including palatability of the product.

In addition this section of the guideline has been amended to reflect on importance of the choice of the method to be used for confirmation of the patients' acceptability.

Note:

Comments on other sections of the guideline (not included in the list above) will not be considered during the review of comments from the second consultation.

Guideline on pharmaceutical development of medicines for paediatric use

Table of contents

Executive summary

The “Paediatric Regulation” aims to facilitate the development and accessibility of age-appropriate paediatric medicines. This aim should be achieved without subjecting children to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age groups.

Critical objectives for the development of age-appropriate paediatric medicines is to ensure that children in the target age group(s) will have access to medicinal products with a positive benefit - risk balance, of a consistent quality, assuring adequate patient’s adherence and which do not put an unnecessary burden on the patient and/or its caregivers.

This guideline is intended to provide additional guidance for the pharmaceutical development of medicinal products for children from birth to less than 18 years of age. This guideline should be read in conjunction with all other relevant EU legislative and guiding documents (see section 3). The guideline takes due account of the scientific and technical progress in the manufacture and control of paediatric medicines at the date of coming into operation.

1. Introduction (background)

On the 26th of January 2007, the “Paediatric Regulation” entered into force (Regulation EC No 1901/2006 of the European Parliament and of the Council, amending regulation EEC No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation EC No 726/2004). This regulation aims to “facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations”. As a result of the aforementioned, it is expected that the number of authorised paediatric medicinal products and the knowledge on the quality aspects critical to these products will rapidly increase.

The physical, metabolic and psychological processes inherent to growth from birth into adulthood reveal that children can not be regarded as small adults nor can they be regarded as a homogeneous group in themselves. As a consequence, clinical trials in adults are not necessarily predictive for children. Thus, in many cases clinical trials will be needed in children of different ages in order to demonstrate that a paediatric medicine is safe and effective in all of the target age group(s) for which the medicine is being developed.

In addition, the treatment of children with medicines poses specific pharmaceutical problems which have not been seen to the same extent in adults, and which occurrence may be age dependent. For example, infants are simply unable to swallow conventionally-sized tablets, newborn infants may require very small volumes of a parenteral medicinal product in order to avoid a volume overload, etc. Therefore, children should be treated with medicinal products the pharmaceutical design of which should be appropriate for use in the target age group(s) i.e. age appropriate paediatric medicines.

Acceptance of and preference among the different dosage form(s) is known to vary between children. The child age, individual health status, behaviour, disabilities, background and cultures are currently considered as the most likely parameters determining the child’s acceptance and preference. However, the initial pharmaceutical development of a paediatric medicine should focus on a minimum number of acceptable dosage forms which are capable of meeting the needs of the majority of the children in the target age group(s). Therefore, dosage forms which facilitate the administration of a range of doses and that are acceptable to children of different ages are helpful for meeting a broad range of children’s needs.

This guideline intends to balance between predictable and consistent regulatory assessments of paediatric medicines (either generic, innovative, existing or new), the speed of development, industrial feasibility and the need to develop medicinal products that are more appropriate for use in children than continuing the practice of unapproved, pharmacy compounded medicines and off-label use.

2. 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. While taking into account that the regulation of medicinal products must be fundamentally aimed at safeguarding public health, it is important to realize that this aim must be achieved by means that do not impede the free movement of safe medicinal products within the European Union.

As clinical evidence and pharmaceutical knowledge increase over time during the development and further life cycle of a medicinal product, the context of the pharmaceutical design of the paediatric medicine in an early clinical trial may differ from the context in the final trials for marketing authorisation. In early development, it is important to focus on the suitability and safety of the proposed formulation/preparation. If the company is not yet able to propose a paediatric medicine, at least considerations for the choice of route(s) of administration, dosage form(s), dosing needs/flexibility and excipients in the formulation/preparation and administration devices should be discussed, including palatability. The use of preliminary (also called enabling) paediatric formulations/preparations in early clinical trials may be considered acceptable if appropriately justified, however it is not exempting from the requirement to develop a formulation/preparation which will be industrially-manufactured and controlled, which is the objective of the Paediatric Regulation. Thus, preliminary formulations/preparations which are based on instructions for pharmaceutical handlings of an authorised medicinal product will normally not be considered acceptable for marketing authorisation, unless sufficiently justified and appropriately validated. A switch from a preliminary formulation/preparation to a commercial formulation/preparation should often be supported by relevant bridging studies between different formulations/preparations used throughout the development.

As knowledge increases, the usefulness (practicality), quality, safety or efficacy of authorised paediatric medicines should be re-evaluated by pharmaceutical companies in the interest of children and their caregivers. This approach is in accordance with Art 23 of the Directive 2001/83/EC which requires that companies take account of scientific and technical progress during the life cycle of a product and adapt or improve their products for the benefit of patients and to maintain a positive benefit-risk balance.

This guideline will not describe any aspects of the pharmaceutical development of a paediatric medicine that equally applies to medicines for adult use. This guideline should not be regarded as providing exhaustive information and does not preclude the existence of other aspects relevant to the pharmaceutical development of paediatric medicines. Any deviation from the guideline is acceptable, if appropriately justified by the pharmaceutical company. The examples listed should not be regarded to reflect the only possible options.

3. Legal basis

This guideline should be read in conjunction with Directive 2001/83/EC of the European Parliament on the community code relating to medicinal products for human use as amended (further referred to as the Medicines Directive), Regulation 1901/2006/EC of the European Parliament and of the Council on medicinal products for paediatric use as amended (further referred to as the Paediatric Regulation) and the European Pharmacopoeia.

In addition, this guideline should be read in conjunction with all other relevant directives and regulations, and relevant Commission, ICH and CHMP guidelines, Q&A documents and other documents as linked to or published on the EMA website (www.ema.europa.eu).

4. General considerations

Any medicinal product should be designed to meet a patient's needs and to consistently deliver the intended product performance. A systematic approach to pharmaceutical development in accordance with ICH Q8 could be followed in order to meet these objectives. When applied, the quality target product profile (QTPP) should be established taking into account the specific needs of the paediatric population. Based on the QTPP the critical product quality attributes should then be identified (CQAs) as well as the formulation and process parameters that may affect them. This approach will help defining the pharmaceutical design of the pediatric medicine.

The pharmaceutical design of a medicinal product relates to all aspects as described in Module 3 of the common technical document (CTD), the summary of product characteristics (SmPC) and the package leaflet (PIL), e.g. the composition of the product, the choice of the dosage form, the selected primary and secondary packaging, etc.

In deciding on the appropriateness of the pharmaceutical design of a paediatric medicine, in addition to the aspects discussed in sections 6 – 12 of this guideline, the following should also be considered:

- the minimum age of the target age group(s), the relevant developmental physiology and the age characteristics of children in the target age group(s);
- the condition to be treated and the condition related characteristics of the child (e.g. children with physical or mental disabilities, under fluid restriction, with a high degree of co-medication, unable to swallow due to critical illnesses);
- the 'criticality' of the dose (i.e. steep dose/pharmacodynamic response curve, narrow therapeutic window), the dosing regimen (i.e. dose calculation, dose titration, flexibility of dosing);
- the age associated activities of children in the target age group(s) (e.g. school, nursery);
- the maximum duration of the therapy and the dosing frequency;
- the environment setting where the product is likely to be used (e.g. hospital or community);
- the child and caregivers characteristics and their behaviour.

5. Characteristics of the active substance

The physico-chemical characteristics of a particular active substance may be desirably modified by the choice in which the active moiety is manufactured into a paediatric medicine as the active substance. For example in some cases the manufacture of a liquid medicinal product may require a substance with improved solubility e.g. a different salt, or a salt instead of the base. Also, child acceptability may be

favoured by the selection of a less soluble form of the active substance to overcome taste issues, e.g. the base instead of the salt. Moreover, patient safety in children may be improved by avoiding particular salts, e.g. mesylates.

At an early pharmaceutical development phase, it is recommended that the selection of the form of the active substance (acid/base, salt, polymorph, solvate etc.) takes into consideration the properties affecting development of paediatric medicines. The selected form of the active substance should enable development of an age-appropriate paediatric medicinal product for use in the target age group(s). The form of the active substance selected for development of a paediatric formulation may differ from the one that is employed for adults.

6. Route of administration and dosage form

6.1. General considerations

The rationale for the choice and advantages and disadvantages of a particular paediatric dosage form via a particular route of administration should be discussed and justified for children in each of the target age group(s). Aspects to be considered include at least the condition(s) to be treated, the treatment duration, the properties of the active substance, the necessity of particular excipients in a paediatric preparation (and their safety), any measuring and administration devices, stability issues, dosage requirements, risk of dosing errors and users aspects such as the ease of administration and patient acceptability.

Different routes of administration and/or dosage forms may be needed for the same active substance in order to ensure adequate treatment of children in all target age group(s), and where relevant with a different health condition, disease development or behavioural characteristics.

The attractiveness of a paediatric medicine should be carefully balanced between the risk of inadequate patient acceptance and accidental intake, and should be discussed with regards to all aspects of the medicine, i.e. the dosage form, the formulation and the primary and any secondary packaging.

6.2. Oral administration

Oral administration can be achieved via several types of dosage forms. In general, the main choice in oral administration is between oral liquid and oral solid dosage forms. The advantages and disadvantages of any oral dosage form/formulation in relation to children in the target age group(s) should be taken into account when selecting a particular dosage form/formulation.

Oral solid single-unit dosage forms may provide a stable and easy dose approach. However, where individually adapted dosing is necessary the number of strengths that are needed to treat patients in the target age group(s) will increase. Alternatives which may provide dosing flexibility for tablets include addition of score lines enabling the administration of a fraction of the full tablet dose or (small) tablets containing only a fraction of the required dose which may be taken simultaneously to deliver the required dose (see section 6.2.1).

Oral powders, granules and liquids normally provide greater dosing flexibility than oral solid single-unit dosage forms. Some oral solid single-unit dosage forms such as dispersible or effervescent preparations are intended to be dispersed, suspended or dissolved prior to administration. Taking part of a liquid prepared from such a dosage form, should normally not be used as means to achieve age-appropriate paediatric medicines. However, the approach may be justified in certain cases, provided that the handling procedure has been appropriately validated including e.g. the ease of preparing the liquid preparation, homogeneity of the resulting liquid and the possibility to withdraw the correct

volume. Multiple step handlings introduce an increased risk for dosing errors, and should generally be avoided.

Children may not be able or willing to swallow a specific dosage form and/or paediatric preparation, even when the dosage form/formulation/preparation itself is generally considered age-appropriate. Therefore applicants are encouraged to investigate the feasibility of bringing different dosage forms/formulations/preparations to the market (e.g. oral liquid as well as tablets). When not feasible, alternative strategies for intake of the preparation should be discussed (see subsection “Handling of dosage forms to facilitate administration” and section 10).

Administration through feeding tubes may be needed for children who are unable to swallow any oral dosage form/formulation/preparation (see section 6.2.3).

6.2.1. Oral solid preparations

Powders and granules

Powders and granules may be given to children from birth provided they can be administered as a liquid. In their solid form, they are usually co-administered with semi-solid food. If mixed with semi-solid food, they can be considered acceptable from the moment the infant is able to accept the semi-solid food, which is usually around six months of age.

The risk of aspiration, choking and where relevant chewing (see section 8) of powders/granules should be discussed in relation to the target age group(s), size, shape and quantity (volume) of the powders/granules and any specific characteristics of the active substance or the formulation.

Administration of powders and granules requires a measuring device unless they are packed in single-dose containers such as sachets (see section 11.3).

Tablets

The tablet size and shape are fundamental to the ability of a child to swallow a tablet. The acceptability of the size and shape of the tablets by the target age group(s) should be justified, and supported by appropriate studies or clinical evidence, where relevant (see section 10). It should be noted that limited data are available in the literature regarding the influence of size, shape and number of tablets on acceptability in different age groups. For chronic diseases, the acceptability of tablets with a particular size and shape in children may be improved by adequate training. Tablet size and shape acceptability may also be improved by adequate instructions for co-administration with semi-solid food. Where tablets are not intended to be swallowed intact, e.g. (oro)dispersible, chewable or effervescent tablets considerations specific to tablet size and shape are of less importance. However, palatability issues may significantly affect the acceptability of these tablet types.

Small tablets containing a fraction of the dose may be considered as a measure to improve both the acceptability and/or dosing flexibility of tablets. These 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 “minitablets”). If a dose requires several tablets to be taken to achieve one dose, the acceptability of the number of tablets which is needed to be taken to achieve a single dose should be discussed and justified for the relevant target age group(s).

Apart from the tablet size and shape, the suitability of tablets in children should be further justified in relation to the different health condition or disease development and the risks associated with under-dosing, choking, aspiration and chewing (see section 8). Relevant warnings should be included in the SmPC and PIL where tablets must not be chewed but must be swallowed intact, i.e. where they may not be chewed. Immediate release tablets are normally intended to be swallowed intact, but unless

otherwise indicated in the SmPC and PIL, they may also in many cases be chewed. Where chewing of immediate release tablets is an option, the potential effect of chewing on the product performance such as palatability should be discussed.

Capsules

Capsules are usually intended to be 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 capsules have been demonstrated. If a hard capsule is to be opened prior to use, its content should meet the same requirements as stated for oral powders or granules, where relevant. The suitability of taking capsules intact or opened should be discussed and justified for all the indicated target age group(s) (see subsection “Handling of dosage forms to facilitate administration”).

As for tablets, limited data in the literature are available regarding acceptability of a certain capsule size in different age groups. Where capsules are to be taken intact, the acceptability of the capsule size and shape, and any associated risks should be considered as indicated for tablets.

Orodispersible and chewable preparations

Orodispersible and chewable preparations involve oral solid unit dosage forms that do not need to be swallowed intact and may be swallowed without a liquid. Orodispersible tablets may be taken by other means than intended i.e. caregivers may disperse the tablet in a liquid prior to giving it to the child or the tablets may be swallowed without dispersion in the mouth.

If there is a risk associated with direct swallowing of an orodispersible or chewable tablet and/or the orodispersible formulation may not be dispersed prior to administration, this should be stated in the SmPC and PIL.

The risk of choking with orodispersible or chewable tablets should be carefully considered as the child may not be able or willing to take the tablets as intended.

Handling of oral solid preparations to facilitate administration

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 such, even when the dosage form is generally considered as age appropriate. In lack of any alternative age appropriate dosage forms, alternative strategies for administering the oral solid preparations should be considered (e.g. dispersing or crushing tablets, mixing with food or drinks). If such an alternative strategy is proposed, the approach should be validated and clear instructions on the handling(s) to be conducted should be given in the SmPC and PIL. Validation of the handling should include aspects such as patient acceptability, dosing accuracy, compatibility with the proposed vehicle, potential impact on bioavailability, and any risks for the person who will handle the dosage form (see section 10).

Score lines are used to enable the administration of a fraction of a full tablet dose or to facilitate breaking for ease of swallowing. The use of score lines in tablets to obtain fractions of the full tablet dose may not be acceptable in all cases due to the criticality of the dose. The ease of breaking a tablet with score line(s) should be demonstrated.

Where appropriately justified and validated, subdivision or crushing of a tablet prior to administration may also be an alternative strategy for administering a tablet to children who have difficulties to swallow the take a tablet intact. It may also be an option to disperse or dissolve a tablet in a liquid prior to intake. In addition, capsules may be opened and their contents given as such. Subdivided/crushed tablets or the contents of a capsule may be given with food or drinks (see Section

10). It may also be an option to disperse or dissolve a tablet in a liquid prior to intake. The suitability of the handling(s), including the compatibility with any proposed vehicle, should be demonstrated.

Where the active substance or dosage form characteristics prevent any handling for the ease of administration this should be clearly stated in the SmPC and PIL.

6.2.2. Oral liquid preparations

General considerations

Oral liquid dosage forms are normally considered acceptable for children from full term birth and for pre-term neonates who are able to swallow and accept enteral feeding. Aqueous liquid dosage forms in multiple-dose containers will normally need to be preserved, whereas oral solid dosage forms will normally not. This would favour the use of oral solid dosage forms over the use of oral liquid dosage forms in children. However, as for any single development aspect, the use of preservatives should not be the only aspect in deciding on the choice between oral liquid versus oral solid dosage forms.

Preserved oral liquid preparations will generally be considered acceptable for children from birth provided that the preservatives (and any other excipients) can be considered safe for children in the target age group(s) (see section 9). For liquid preparations that are prepared by reconstitution from a solid oral dosage form, solvents other than water should be provided as part of the medicinal product. Oral liquid paediatric dosage forms should be packaged together with an appropriate measuring device, unless it has been demonstrated by the company that commercially available measuring devices are suitable for accurate dosing of the recommended doses and that these devices are widely available (see section 11.3). The device should be suitable to measure all recommended doses and the suitability needs to be validated in relation to the actual liquid formulation/preparation. This is particularly critical for viscous oral liquids. The SmPC and PIL should include clear instructions on the correct use of the device to ensure that the recommended dose is taken by the child. If commercial devices are to be used, the type of the device (including any adaptor) should be specified in the SmPC and PIL.

The risks of incorrect or accidental under- or overdosing with the measuring device should be discussed and justified in relation to the criticality of the dose for children in the target age group(s) and the potential for dosing errors when measuring the paediatric medicine. Where incorrect dosing is likely to result in a potential serious risk to children, measures such as a dedicated measuring device, application of unit-dose packaging or the selection of another dosage form should be considered.

The volume of the dose of an oral liquid preparation may have an impact on the patient acceptability. Small volumes are normally better tolerated for preparations with known palatability issues, unless a more diluted preparation may allow better taste masking.

Oral suspensions

Critical product quality attributes to be considered for oral suspensions include physico-chemical characteristics of the suspension such as viscosity, potential for foaming, air entrapment, sedimentation and sticking of the suspended active substance to the primary container and to the measuring device. Where sedimentation cannot be avoided, easy re-suspension with moderate shaking is recommended to reduce the risk of insufficient shaking and dosing errors due to inhomogeneous distribution of the active substance.

The risks of under-dosing and over-dosing to the child if not shaking the container properly or not shaking it at all should be discussed. Clear instructions on correctly withdrawing the dose should be included in the SmPC and PIL, including warnings if incorrect shaking may lead to over- or under-

dosing. Adequate measures should be undertaken in cases where incorrect shaking will result in a potential serious risk to the child's health. Such measures may involve the application of unit dose packaging or selection of a different dosage form.

Oral drops

Oral drops can provide a useful means to administer medicinal products in low doses or small volumes. The risk of counting the incorrect number of drops, and the accuracy and precision of the volume dispensed should be justified in relation to the criticality of the dose. In order to avoid counting errors, alternative measuring devices should be considered where the dose comprises more than 10 drops. Unless otherwise justified, oral drops will only be considered acceptable for paediatric medicines containing active substances with a wide therapeutic window

The volume dispensed (i.e. drop size) will be determined by the design and physical characteristics of the dropper, the physical-chemical properties of the liquid and how the dropper is handled. Clear instructions should be included in the SmPC and PIL on the correct use of the dropper.

Effervescent, soluble and dispersible preparations

These preparations are intended to be dissolved or dispersed in liquid prior to administration. The applicability of effervescent preparations for use in children may be restricted by the relatively large volume of liquid needed for dissolution and the high electrolyte content.

The minimum volume for dissolution or dispersion and any needed rinse volume(s) should be discussed and justified in relation to the target age group(s). Clear instructions on how to prepare the solution or dispersion in a correct manner should be given in the SmPC and PIL. These instructions should include information on the minimum volume for dissolution or dispersion, including any rinse volume(s) and any specific requirements for stirring or mixing.

Similar to considerations for orodispersible and chewable preparations, the potential risks when administered without prior dispersion or dissolution should be considered. Any issues related to alternative modes of oral administration should be clearly stated in the SmPC and PIL.

6.2.3. Administration through feeding tubes

Oral medicinal products are likely to be administered via a feeding tube to patients who are tube fed, due to their condition or age related limitations e.g. pre-term neonates, unable to swallow but able to receive enteral feeds.

Where administration through feeding tubes is used, either as a main route or as a very likely option, the feasibility of administration through the feeding tube needs to be addressed. The particle size, viscosity, dosing and rinse volume(s), chemical compatibility of the oral medicinal product with the tube material and the risk of physical blockage of the tube should be considered during pharmaceutical development. Dose recovery after extrusion needs to be demonstrated using feeding tubes and rinse volumes relevant to the target age group(s).

In addition, and if relevant depending on the location of the tube, the risks associated to the accidental aspiration of the medicinal product and the possible effect on the bioavailability should be discussed.

Where administration through feeding tubes is highly likely, the SmPC and PIL should provide information if the medicinal product can (or cannot) be administered through a feeding tube, including instructions on the correct procedures.

6.2.4. Oromucosal preparations

The correct use and acceptability of oromucosal preparations will depend on the age of the child and the ability to keep the preparation in a specific part of the mouth over a defined period of time. The adhesive properties of oromucosal preparations should be discussed in relation to the local area where they should be applied. In order to avoid the risk of swallowing mouthwashes or dental gels, these dosage forms need to be applied in young children using a cotton bud, sponge or similar applicator.

6.3. Nasal preparations

Nasal preparations will normally be considered suitable for children of all ages. The suitability of the nasal route of administration for local and systemic treatment with a particular paediatric medicine should be discussed and justified in terms of the likelihood that the active substance (and excipients) will cause pain or irritation. The use of any preservative should be justified as outlined in section 9. Also, the patient acceptability should be discussed in relation to the palatability and sensation of the medicinal product on actuation.

For nasal preparations with a local action, the risks of systemic (adverse) effects should be discussed. Devices for nasal administration should be suitable for the size of the nostrils/nasal cavity, including the delivered volume, for the target age group(s).

6.4. Preparations for inhalation

The patient acceptability and age-appropriateness of orally inhaled paediatric medicines (including solutions for nebulisation) need to be justified.

Pressurized metered dose inhalers may be applied to children from birth if in combination with a specific spacer system and face mask. Older children may use the inhaler with or without a spacer. Companies should justify the suitability of the proposed equipment for use in the target age group(s).

Unless appropriately constructed, dry powder inhalers can only be applied by older children because it is the child patient who makes his or her dose by the inspiratory flow.

6.5. Rectal preparations

Suppositories

The size (length and diameter) of the suppository should take into account the age and size of the child. Unless suppositories have been specially designed to deliver smaller amounts of the full dose, they should not be cut in order to provide a smaller dose, due to the high risk of dosing errors related to inhomogeneous distribution of the active substance and difficulties in reproducible cutting.

Liquid rectal preparations

The length of the rectal tube of the enema and any volume to be administered should take into account the age and size of the child. The use of scaled devices (pre-filled syringes with a rectal tip) should be considered where relevant. Clear instructions should be provided in the SmPC and PIL on the method for delivering the required dose to the child by the caregiver.

6.6. Cutaneous and transdermal preparations

Developmental changes in barrier function of the skin, such as dermis thickness, hydration and perfusion of the epidermis and the changing ratio of body surface area to weight, should be taken into consideration when developing cutaneous and transdermal preparations for children.

The use of excipients known to sensitize the skin (e.g. some surfactants and adhesives) should be carefully considered and justified. The need or restriction to use water-impermeable or other types of materials as a coating to the cutaneous medicinal product should be clarified. Where relevant, the impact of occlusion, fever or thermal heating on skin permeability and the risk of overdosing should be discussed.

The size and shape of transdermal patches and medicated plasters should be tailored to the size and shape of the child body and should not interfere with daily routines. Application sites which cannot be easily reached by the child are preferred in order to avoid that the patch can be removed by the child. If sites reachable to the child are to be used, the impact of deliberate removal of the patch/plaster on the clinical outcome should be discussed.

Patches and plasters are preferably developed for use without the need for cutting to achieve a smaller dose, i.e. developed in a sufficient range of age-appropriate sizes or strengths. However, some types of patches (e.g. matrix types) may be developed to provide for a range of doses/strengths by cutting. Cutting will only be considered acceptable if clearly marked cutting lines are present and if dose uniformity and consistency of delivery properties have been appropriately demonstrated.

Information whether the patch can (or cannot) be cut to provide a smaller dose needs to be included in the product information, with clear instructions how lower doses can be obtained by cutting along to the marked lines. Instructions should also be provided for safely discarding the (cut) patch, or the potential to use the remaining parts of the patch after cutting.

6.7. Eye and ear preparations

Preparations for the eye and ear are mostly developed for a single patient group, including children, adults and the elderly. Preparations for the eye and ear may be poorly accepted by some children. However in lack of better alternatives they should be considered acceptable dosage forms for children of all ages.

In order to avoid the use of preservatives with potential local toxicity to the cornea and/or mucous membranes, single dose preparations or multi-dose preparations in a dedicated multi-dose container that does not require its contents to be preserved i.e. preservative free containers should be considered for children, especially neonates. This is especially important if long term use may be necessary.

Young children can not yet be instructed to keep their eyes open. It is important that the parent is informed as to how to hold container and the child in order to correctly administer the paediatric medicine.

6.8. Parenteral administration

General considerations

Parenteral administration is the most commonly used route of administration for active substances for children who are seriously ill and for clinically unstable term and preterm neonates.

The choice for an intravenous, subcutaneous or intramuscular injection is to be justified in terms of the intended clinical effect, relevant characteristics of the active substance and child acceptance (pain).

The route of intravenous administration (central or peripheral), site of injection, the injection volumes, the rate of administration, the viscosity, pH, buffering, osmolarity and, if relevant, the needle thickness and needle length should be described and justified towards the characteristics of the parenteral preparation, the age and weight of the child, the maximum number of injections per day and the duration per treatment. Where appropriate, the use of micro-needles or needle free injectors could be considered, especially for medicines requiring frequent or long treatment periods.

Serial dilutions (in order to achieve the required dose) are not acceptable as they are prone to errors and can be avoided by providing appropriate concentrations of the parenteral medicine.

The minimum dosing volume of a medicine will depend on the accuracy of the relevant measuring device. Where relevant, the size of the syringe and the graduation that permits accurate administration should therefore be described as well. The volume should be justified according to the age of the children. Normally, subcutaneous and intramuscular injection volumes should not exceed 1 ml however for neonates and small infants lower volumes are warranted. Some parenteral preparations may be intended for emergency situations where venous access may not be easily established (e.g. resuscitation and intensive care). The suitability of medicines which are commonly used in emergency situations for intra osseous administration should be discussed and relevant information should be provided in the SmPC and PIL.

Neonates may only accept very small volumes of medication in order to avoid volume overload and to allow sufficient room for essential fluid nutrition. Infusions must not be so concentrated that the appropriate dosage rates are not feasible by using standard pump equipment. These aspects should be considered in particular to medicines intended to be administered as a continuous infusion. In addition, specific concerns related to incompatibility with co-administered medication in the infusion line, osmolarity, inappropriate diluents, and potential for over- or under-dosing due to lag-volume effects in iv fluid lines should be investigated during the development.

Out-patient use

In cases where parenteral administration is required for children in out-patient settings, it should be demonstrated that the presentation of the parenteral medicine is suitable for administration by the child itself or its adult caregiver. This is especially important in cases where administration may also be necessary in situations where a trained caregiver is not present.

6.9. Fixed dose combinations

Fixed dose combinations are often developed as an alternative substitution therapy for patients already treated with the individual components, especially for chronic diseases such as HIV or tuberculosis. They may be of value for patients to simplify therapy and improve adherence. When clinically relevant, the company should make efforts to consider all possible options for developing an age-appropriate fixed dose combination for all or some subsets of the paediatric population, unless such a development would be prevented by the complexity of doses required or by the lack of flexibility to ensure an adequate dose adjustment.

7. Dosing frequency

The choice of the dosing frequency should be justified in terms of the characteristics of the active substance, the pharmacokinetic profile, the indication and the child patient and caregiver

convenience/therapeutic adherence. Taking into account these criteria, a maximum twice daily dosing is preferred for out-patient use. For paediatric medicines that may be used more than twice daily, special attention should be given to the suitability of administration in out-patient settings where a trained caregiver is not readily available (kindergarten, school, etc.).

8. Modified release preparations

Modified release medicinal products should be considered for children when relevant. The development of modified release preparations should not be restricted to the oral route of administration. Alternative routes of administration could be applicable depending on the active substance characteristics (e.g. transdermal).

Prolonged release formulations can be useful for children who would otherwise need to take medication whilst at school or during the night. Their use can reduce the dosing frequency significantly and can be beneficial for compliance.

For oral solid modified release preparations, the risk of chewing is to be considered when selecting this dosage form for further development. The risk of chewing and its impact on the efficacy and safety of the medicinal product should therefore be discussed and it should not result in a serious risk to patients.

In the development of oral modified-release preparations for paediatric use, attention should be given to the physiological conditions related to the age of the child to be treated, e.g. gastric pH and gastro-intestinal motility (gastric emptying, transit time) and their variability since these characteristics could have an impact on the drug absorption.

9. Excipients in the formulation

9.1. General considerations

The choice of a suitable excipient in a paediatric medicinal product is one of the key elements of the pharmaceutical development.

Although the basic considerations regarding the use of a specific excipient are similar for adult and paediatric medicines, the inclusion of any excipient in a paediatric medicinal product requires additional safety consideration. The intake of an excipient may result in a different exposure in children than in adults and the excipient may have a different effect on developing organ systems. Due to the limited safety data relevant to the use of an excipient in a specific age group a precautionary approach should be followed.

Overall, the following aspects are to be considered with respect to the selection of an appropriate excipient for paediatric medicines:

- the function of the excipient in the formulation and potential alternatives;
- the safety profile of the excipient for children in the target age group(s) on the basis of single and daily exposure (and not the concentration or strength of the medicinal product);
- the expected duration of the treatment i.e. short term (single dose/few days) versus long term (weeks, months, chronic);
- the severity of the condition to be treated (e.g. life-threatening disease) and the therapeutic alternatives;

- the patient's acceptability including palatability (e.g. taste, local pain);
- allergies and sensitization.

In case the use of excipients with an identified risk cannot be avoided in the formulation of a particular pharmaceutical dosage form, the added value of the chosen pharmaceutical dosage form (and route of administration) should be well balanced against the possible use of other pharmaceutical dosage forms and routes of administration that do not require the use of such excipients. Comprehensive development rationale should be provided, taking into account the relative benefits and risks of possible alternatives.

New evidence may suggest that there could be safety issues related to excipients used in authorised paediatric medicines, either as such, above a specific daily intake or for distinct target age group(s). In these cases, as a precautionary measure, pharmaceutical companies are recommended to avoid excipients with a potential cause for concern in newly developed paediatric medicines until further research allows scientifically justified conclusions to be drawn on their safety.

Whilst it is acknowledged that the use of a novel excipient (i.e. an excipient used for the first time in a medicinal product or by a new route of administration) is fundamental to pharmaceutical innovation and that the use of such novel excipients may be well justified by appropriate pre-clinical studies, it must be realized that safety issues may only become apparent when the paediatric medicine is used on a larger scale. Therefore, the added value of the novel excipient in a specific paediatric medicine must be well balanced against the use of other excipients with an established safety profile, other dosage forms or routes of administration.

Allergies can arise from early childhood and children may be more easily sensitized than adults. In order to avoid sensitization and to expand treatment possibilities of allergic children, applicants should consider avoiding, where possible, excipients with known potential to cause sensitization/allergies.

The following information sources (listed in hierarchy) should be consulted in order to assess the safety profile of each excipient in a paediatric formulation (see Figure 1) resulting in an overall conclusion as to whether or not additional data are needed:

- Commission, ICH and EMA guidelines;
- CHMP scientific opinions (e.g. CHMP Position paper, CHMP Opinion on a referral procedure);
- Qualitative composition of an excipient in medicinal products currently authorised for use in children, and their quantitative composition if known;
- Food Legislation.
    - This source of information poses some limitations as it relates to food only (i.e. chronic and long term oral use);
    - All relevant excipients described in the Food Legislation as suitable for the paediatric population are normally considered acceptable for use in oral paediatric medicines unless there are additional safety indications from the other information sources and unless the wording in the Food Legislation itself causes reason for concern. In case of such additional concerns, the excipient should either be omitted from the formulation or the applicant should justify why the inclusion of the excipient can be considered acceptable;
    - The aforementioned does not apply to neonates for which further non-clinical data will normally be required;

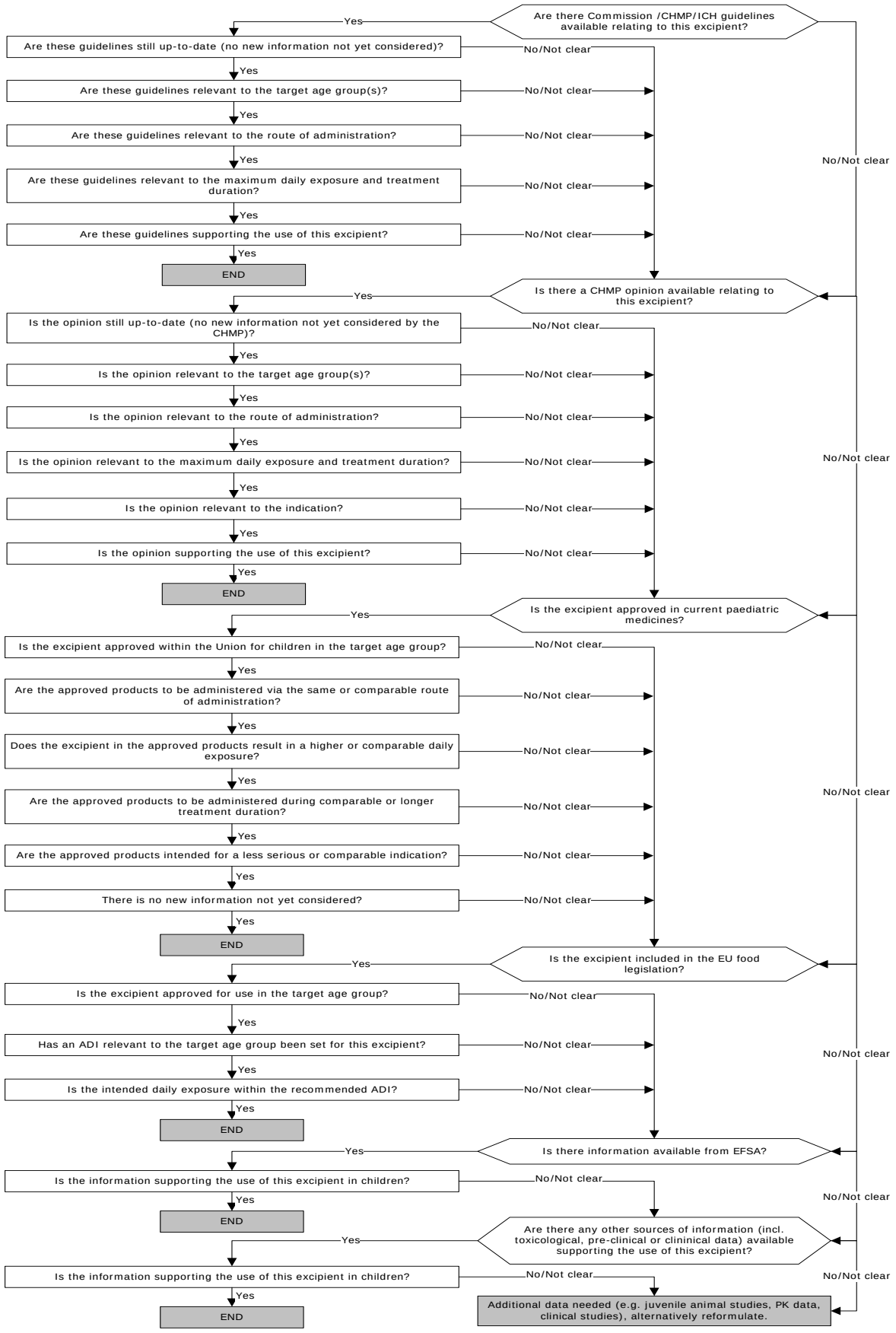
- The safety of relevant excipients described in the Food Legislation requires further evaluation for use in non-oral dosage forms;

- The European Food Safety Scientific Opinions (EFSA).
  - This source of information poses some limitations as it relates to food only (i.e. chronic and long term oral use) and the data may not relate to children. However a warning for adults should question the safety of the excipient for use in children.
- Other sources of information as e.g.
  - Expert committee on food additives (JECFA), which is a mixed committee of the WHO and the Food and Agricultural Organisation;
  - Information in indexed literature;
  - In-house information as non-published scientific evidence.

The relevance of acquired data for the excipient in the proposed paediatric medicinal product should be summarised and discussed in relation to the age groups, indication, route of administration and type of dosage form, treatment duration, maximum daily intake of the excipient and exposure.

It is emphasized that it is the responsibility of the applicant to justify that each excipient in the paediatric medicine is safe for its intended use in target age group(s). Toxicological studies may be necessary if the use of an existing excipient in a paediatric medicine can not be justified on the basis of the aforementioned information sources.

Figure 1: Points for consideration in the evaluation of the safety profile of excipients in paediatiric formulations for a specific target age group



END = no further need to justify the use of the particular excipient in the paediatric medicine (when the excipient or the medicinal product meets the conditions stated)

597

9.2. Colouring agents

The use of any specific colouring agent in a paediatric medicine should be discussed and justified in terms of allergenic potential, minimal toxicological implications in the target age group(s), child patient acceptability and the need to avoid accidental dosing errors. Where there is a need to differentiate between similar medicinal products to avoid accidental dosing errors, the use of e.g. shape, size and embossing should nonetheless be considered prior to considering the use of colouring agents. The justification should address both the necessity to colour the medicinal product and the selection of a particular colouring agent.

Unlike other excipients, the use of colouring agents in medicinal products is governed by a specific directive (Directive 2009/35/EC of the European Parliament and of the Council of 23 April 2009 on the colouring matters which may be added to medicinal products).

9.3. Flavours

Adequate palatability plays an important role in patient acceptance. Especially in oral liquid formulations, flavours may be necessary to achieve this goal. The rationale for the use of a particular flavour in a paediatric medicine should be clearly described and justified. The qualitative and quantitative composition of any components of the flavouring agent that are known to have a recognised action or effect should be provided. Safety concerns should be discussed, including the risk of allergies and sensitization.

9.4. Preservatives

The use of preservatives is normally considered acceptable in multidose preparations, however for many preservatives there is still limited data regarding the levels of safe exposure in children. The need to preserve the paediatric medicine and the choice of the preservative system at the lowest concentration feasible should be justified in terms of risk to benefit balance.

The appropriateness of the preservative system for the target age group(s) should be discussed. Unless safety data relevant to children is available, applicants should justify the level of exposure (proposed safety margins) taking into consideration thresholds for adults and also consider the possibility of alternative dosage forms.

Pharmaceutical companies are encouraged to consider novel strategies that allow the preservative-free formulation of paediatric medicines.

9.5. Sugars and sweeteners

Adequate patient's acceptability of oral paediatric formulations is paramount and sweetness plays an important role in this.

The rationale for the use of a particular sweetening agent in a paediatric medicine should be clearly described and justified. Safety concerns should be discussed, including conditions that would restrict the use of a particular sugar or sweetener (e.g. diabetes, severe renal insufficiency).

The choice and concentration of sweetening agents depends on the properties of the active substance and the use of flavours.

The use of cariogenic sugars should be carefully justified. Frequent and/or high doses of sweetening agents should preferably be avoided in paediatric formulations intended for long term use. The potential laxative effect of polyols (e.g. sorbitol, mannitol) should be considered. The osmotic

properties of polyols might also affect bioavailability. It should be noted that limited data are available on the relevant thresholds for polyols in children.

Alternative approaches with taste improvement (coating, complex formation, choice of vehicle, adjustment of viscosity) should be considered where relevant.

10. Patient acceptability

Patient acceptance can be defined as the overall ability and willingness of the patient to use a medicinal product as intended and its care giver to administer the medicine as intended. Patient acceptability is likely to have a significant impact on the patient's adherence and consequently on the safety and efficacy of the medicine. It is determined by the characteristics of the medicinal product and the user. The product aspects involve the pharmaceutical characteristics of the medicinal product such as:

- palatability, swallowability (size and shape);
- complexity of handling to be conducted by the child or its caregivers prior to administration;
- the required dose e.g. the dosing volume, number of tablets etc.;
- the required dosing frequency;
- the selected administration device;
- the primary and secondary container closure system;
- the actual mode of administration to the child and any related pain or discomfort.

Evaluation of the patient acceptability of a paediatric medicine should be an integral part of the pharmaceutical development studies. Patient acceptability of the medicinal product should be studied in children themselves as part of any clinical study involving the proposed product. In justified cases where no clinical studies will be conducted or in justified cases where patient acceptability will not be studied in the clinical studies, the adequate patient acceptability of the medicinal product(s) as proposed for marketing should be demonstrated otherwise e.g. by literature references or by studies in dedicated adult panels. Oral liquid preparations are generally considered acceptable from birth however the perception of palatability evolves and becomes critical.

For authorised medicinal products for which acceptability of the current formulation was tested during the development the adequate patient acceptability should be assured. In cases of variations to the composition of authorised formulations the impact of the change should be evaluated by the company and the acceptability should remain to be assured.

Adequate patient's acceptability is not to be understood as 100% acceptance of a medicine by children in the target age group(s). Moreover, different methods to measure patient's acceptability may result in different outcomes. Therefore the suitability of the chosen method to test the patient' acceptability and the appropriateness of the limits to be applied should be discussed and justified in terms of risk to benefit considerations, including risks at population level (e.g. emergence of microbiological resistance due to poor acceptability of different preparations with antibiotics), and should take account of the characteristics of the target age group(s), the condition relevant to the paediatric medicine, incidental and multiple use, co-medication.

Palatability

Palatability is one of the main elements of the patient acceptance of an oral paediatric medicine. It may also be an aspect related to the use of nasal and inhalation medicines. Palatability is defined as

the overall appreciation of an (often oral) medicinal product towards its smell, taste, aftertaste and texture (i.e. feeling in the mouth). It is determined by the characteristics of the active substance and the way the active substance is formulated into a finished medicinal dosage form. Information on the palatability of the active substance should consequently be acquired at an early stage in the development of a medicinal product, e.g. from dedicated adult panels and literature. The palatability of the active substance should contribute to the choice of the selected finished dosage form(s) and route(s) of administration. Unless otherwise justified, the palatability of a paediatric medicine should be satisfactory on its own merit (i.e. without mixing with food or drinks).

A paediatric medicinal product with a neutral taste or a paediatric medicinal product with a specific and generally acceptable taste may be developed. The choice for either of these profiles should be justified. Normally, development of medicinal products with a neutral taste should be considered, especially for paediatric medicines used in the treatment of chronic conditions as strong flavours can become unpalatable with repeated administration. The development of the intended target palatability (neutral or a specific taste) should be clearly described and include information on relevant alternative compositions or dosage forms.

Examples of measures that can be undertaken to improve the palatability of a medicinal product include a judicious choice of excipients (including taste maskers, sweeteners and flavouring agents), change in particle size of the active substance or of excipients, choice of a different salt of the active moiety, coating of the active substance, coating of the finished dosage form, use of a complexing agent (e.g. cyclodextrines) or for liquid preparations: lowering the amount of free active ingredient in solution by choice of a different strength and subsequent change in volume. However, paediatric formulations/preparations must not become too attractive to children (candy like) as this is known to increase the rate of accidental poisoning.

Mixing with Food

For a variety of reasons it may be desirable to mix a paediatric medicine with food and drinks. Whatever the reason the rational should be explained and justified. Mixing with foods or drinks may either be intended to mask the unsatisfactory taste of a medicinal product in cases where it has been demonstrated that the palatability of the paediatric medicine cannot be further improved and where alternative dosage forms can not be developed.

Mixing recommendations can also be applied as a further means to improve the patient acceptability and the ease of swallowing of an otherwise already palatable medicinal product. Moreover, the lack of recommendations on mixing with foods or drinks will not assure that caregivers will not employ this method in order to administer the medicine. Therefore, the effect of mixing the medicinal product with certain type(s) of common foods or drinks for children should be discussed and/or studied for every paediatric medicine. The SmPC and PIL should always contain clear information if the product can or cannot be mixed with foods or drinks. If mixing with foods or drinks is not recommended the SmPC and PIL should clearly state that the mixing of the medicinal product with food or drinks has not been studied and is the responsibility of the user.

In addition, appropriate warnings should be added in cases where incompatibilities with certain type(s) of foods and drinks are foreseen. If mixing with foods and drinks is recommended, the type(s) of foods and drinks should be clearly indicated including any temperature conditions where relevant. The user should be instructed that the medicinal product should be mixed with a small portion (e.g. one spoon) or otherwise justified quantity of the food or drinks, and needs to be taken within clearly specified time after mixing. In exceptional cases larger quantity may be necessary to assure adequate palatability or dissolution. Large amounts of food or drinks (e.g. one full glass/meal) should however be avoided because of the risk that the child may not be able or willing to take the full quantity.

Different foods or drinks may have different properties and differ in their effect on the medicinal product. Any choice should be justified in terms of their effects on the properties of the paediatric medicine. It is understood that food and drinks are usually not standardized products and that the whole range of variability cannot be covered by patient's acceptability and compatibility studies. Nevertheless the SmPC and PIL should give clear instructions on what foods and drinks have been demonstrated to be appropriate for the medicinal product to be mixed with. Unless otherwise justified, information on the stability of the product in the recommended foods should be provided. This information should include information on any restrictions on the temperature of the food stuffs. Some medicinal products may dissolve or partially dissolve in foods. This may affect product performance and the pharmacokinetic behaviour.

When mixing with food and drinks is proposed the possible effect on biopharmaceutical characteristics of the product should be discussed. Bioavailability testing may be needed depending on information that is available from previous studies relevant to the paediatric medicine.

11. Container closure system, measuring device, administration device and packaging

11.1. General considerations

The container closure system and administration device should be designed for use in the target age group(s). When used together they should allow the appropriate use of the preparation.

Unless otherwise justified, container closure systems used in adolescent children should be discrete and portable and, where reasonable, enable individual doses to be taken to school, sports etc. Where relevant, the SmPC and PIL should state that the medicinal product should only be used in combination with a designated administration device.

Pharmaceutical companies are encouraged to consider novel packaging and administration strategies that improve child acceptance, child adherence and child and/or caregiver's convenience whilst reducing the risk of accidental dosing errors.

The container closure system should differentiate the medicinal product from confectionary and toys to reduce the attractiveness of the product to children.

The practicality of the container closure system and administration device should be considered. For example, some bottles used for oral liquid medicine are small enough to allow removal of the entire contents with an oral syringe of appropriate length. Other containers will require a "syringe adaptor", which is an integrated bung in the neck of the bottle into which the oral syringe fits. The syringe adaptor allows the entire contents of the bottle to be successfully removed form the bottle.

11.2. Container size

General considerations

The full contents of a container should be justified in terms of

1) dosing recommendations and dosing duration in the SmPC and PIL for each of the target age group(s);

2) accidental dosing errors, specially the risk of 10-fold overdosing;

3) accidental ingestion of the full contents;

4) patient acceptability.

11.3. Measuring device

Specific attention should be given to the ease and accuracy of the administration. The 'criticality' of the dose i.e. steep dose/pharmacodynamic response curve, narrow therapeutic window should also be discussed.

Unless otherwise justified liquid paediatric medicines should be supplied with a measuring device. The physical characteristics of the liquid preparation in relation to the measuring device will play a part in determining the accuracy of dosing. The combination of the paediatric preparation and the measuring device should be investigated in order to ensure accurate dosing.

There may be situations where it is claimed that it is not necessary to supply a measuring device with the paediatric medicines. In these cases it should be demonstrated that accuracy of dosing is achieved with a range of commonly available measuring devices such as measuring spoons and measuring cups. The user instructions should be specific to the type of measuring devices to be employed.

The age appropriateness of an administration device should be discussed. An oral syringe may provide a more reliable method of administration for oral liquids in the youngest age groups than a spoon or a cup.

The nominal volume of the measuring device and the graduation on the device should be assessed in view of the recommended doses, the risk of over and under dosing and the availability of a higher or lower strength of the medicinal product. Measuring devices may be used for repeated oral dosing, if appropriately cleaned. A cleaning instruction should be included in the SmPC and PIL.

If a device is specifically designed to deliver the correct doses for a particular product, e.g. a cup to measure a particular number of granules, then the product name should be displayed on the device in order to avoid mixing devices for different medicinal products.

Some measuring devices such as oral syringes may contain some dead space. The significance of the dead space increases as the volume measured decreases. This should be discussed. It should be demonstrated that it is insignificant to accuracy when the intended volume is measured. Incorrect flushing of syringes and needles may result in a relevant overdose of the intended volume for administration. The risk of such overdosing to individual child health should be discussed. In relevant cases, an appropriate warning i.e. not to flush the syringe and needle may be considered in the SmPC and PIL.

The accuracy of measuring devices for paediatric medicines with a steep dose/pharmacodynamic response curve or narrow therapeutic window may require special considerations. Accuracy of such devices should be discussed and justified.

11.4. Other devices

For routes of administration requiring the use of a specific administration device, the appropriateness of the device for the target age group(s) should be justified, e.g. face masks, nebulisers.

Aspects to be discussed include the ease of administration by the child or its caregiver, difficulties in administration to unwilling children, and the robustness of the device in daily practice. Any necessary device should be dispensed with the product unless the applicant can demonstrate that the device is commercially available.

12. User information (summary of product characteristics and patient information leaflet)

Pharmaceutical companies should provide clear user instructions that favour the correct and full administration of their paediatric medicinal products. These instructions should take account of the different administration scenarios to children from birth into adulthood. Where relevant, instructions that are both suitable for the caregiver as well as the child are strongly recommended. User instructions should be sufficiently robust towards unwilling children, especially where full adherence is critical for therapeutic outcomes.

Detailed instructions can be found in the Guideline on the SmPC.

Definitions

Age-appropriate paediatric medicine

A medicine the pharmaceutical design of which is suitable for use in the target age group(s).

Preliminary formulation (as called enabling formulation)

A preliminary formulation is relatively simple and easy to prepare formulation that facilitates the preclinical and/or early clinical development studies which might otherwise be delayed whilst developing the final age-appropriate paediatric medicinal product.

Paediatric formulation

The composition of a particular dosage form of a medicinal product for paediatric use.

Paediatric preparation

A paediatric formulation in a particular strength (e.g. tablets 5 mg, solution for injections 5 mg/ml) and, in case of paediatric formulations for single use, the labelled container contents (e.g. solution for injection 5 mg/ml, 1 ml = 5 mg or 2 ml = 10 mg).

Paediatric medicine / paediatric medicinal product

A paediatric preparation in its container closure system, together with any measuring and administration device and the user instruction.

Pharmaceutical development

In the context of this guideline, pharmaceutical development relates all aspect as described in Module 3.2.P of the Common Technical Document, the user instruction in the SmPC (section 6.0) and the PIL. It is defined as the process of turning an active pharmaceutical moiety into a paediatric medicinal product that is suitable for administration by the child itself or its adult caregiver, including all related pharmaceutical aspects as e.g. the control of raw materials, the validation of analytical methods etc.

Pharmaceutical design of a medicinal product

The composition, dosage form, route of administration, dosing frequency, packaging, measuring or administration device and the user instruction of a medicinal product.