EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Guideline on pharmaceutical development of medicines for paediatric use

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
Final version agreed by QWP	June 2013
Final version agreed by PDCO	July 2013
Final version adopted by CHMP	July 2013
Date for coming into effect	15 February 2014

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

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 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 between birth and 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). The 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 they can 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 whose occurrence may be age dependent. For example, infants are simply unable to swallow conventionally-sized tablets, neonates may require very small volumes of a parenteral medicine to avoid a volume overload, etc. Therefore, children should be treated with medicinal products whose pharmaceutical design should be appropriate for use in the target age group(s) i.e. age-appropriate paediatric medicines.

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. However, the initial pharmaceutical development of paediatric medicinal products 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). This can be achieved by developing dosage forms which facilitate the administration of a range of doses and that are acceptable to children of different ages.

This guideline intends to strike a 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, rather 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 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 medicinal product 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 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 preparation and administration device(s) should be discussed, taking into consideration acceptability. The use of preliminary (also called enabling) paediatric preparations in early clinical trials may be considered acceptable if appropriately justified. However, it does not exempt the applicant from the requirement to develop a preparation which will be industrially manufactured and controlled, which is the objective of the Paediatric Regulation. Thus, preliminary 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 verified. A switch from a preliminary preparation to a commercial preparation should often be supported by relevant bridging studies between different 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 Article 23 of the Directive 2001/83/EC which requires that companies take account of scientific and technical progress during the life cycle of a medicinal 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 also apply 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 as reflecting 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, 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 all 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 medicine should be designed to meet patient needs and to consistently deliver the intended product performance. A systematic approach to the 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 consideration the specific needs of the paediatric population. Based on the QTPP the critical product quality attributes (CQAs) should then be identified as well as the formulation and process parameters that may affect them. This approach will help defining the pharmaceutical design of the pediatric medicinal products.

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, 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) and 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 caregiver's 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.

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 medicinal products. 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 form that is employed for adults.

6. Route of administration and dosage form

6.1. General considerations

The rationale for the choice along with the advantages and disadvantages of a particular paediatric dosage form and 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 formulation (and their safety), any measuring and administration devices, stability issues, dosage requirements, risk of dosing errors and user 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 profile or behavioural characteristics.

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.

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 liquids and solid dosage forms. The advantages and disadvantages of a given oral dosage form in relation to children in the target age group(s) should be considered when selecting a particular dosage form.

Oral solid single-unit dosage forms may provide a stable and easy dosing approach. However, where individually adapted dosing is necessary, the number of strengths needed to treat patients in the target age group(s) will increase. For tablets, alternatives which may provide dosing flexibility include addition of break marks enabling administration of a fraction of a 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 to allow flexible dosing, 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 procedure has been appropriately verified including e.g. the ease of preparing the liquid preparation, homogeneity of the resulting liquid and the ease of measuring the

correct volume. Multiple step procedures should generally be avoided as they introduce an increased risk for dosing errors.

Children may not be able or willing to swallow a medicinal product, even when the dosage form, the formulation or the preparation is generally considered age-appropriate. Therefore applicants are encouraged to investigate the feasibility of bringing different dosage forms, formulations or preparations to the market (e.g. oral liquid as well as tablets). When this is not feasible, alternative strategies for intake of the medicinal product should be discussed by the applicant (see section "Modification of oral solid preparations to facilitate administration" and section 10).

Administration through feeding tubes may be needed for children who are unable to swallow the available oral medicinal products (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 preparation. In their solid form, they are usually given with semi-solid food (see section 10). If given 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, of powders/granules should be discussed in relation to the target age group(s), size, shape and quantity (volume) of powders/granules and any specific characteristics of the preparation.

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 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. It should be noted that limited data are available in the literature regarding the influence of size, shape and the number of tablets on acceptability in different paediatric 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 lesser importance. However, palatability issues may significantly affect the acceptability of these tablet types.

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).

Apart from the tablet size and shape, the suitability of tablets in children should be further justified in relation to different health conditions or disease development profiles and the risks associated with under- or overdosing, 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. Immediate release tablets are normally intended to be swallowed intact, but unless otherwise indicated

in the SmPC and PIL, they may also be chewed. Where chewing of immediate release tablets is an option, the potential effect of chewing on the product performance and 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 capsule has been demonstrated. If a hard capsule is to be opened prior to use, its content should meet the same requirements as normally applied for the type of the content e.g. granules. The suitability of taking capsules intact or opened should be discussed and justified for all the indicated target age group(s) (see section “Modification of oral solid preparations to facilitate administration”).

As for tablets, limited data in the literature are available regarding acceptability of different capsule sizes in different paediatric age group(s). Where capsules are to be taken intact, the acceptability of the capsule size 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 are not primarily intended to be swallowed intact. 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 preparation may not be dispersed prior to administration, this should be stated in the SmPC and PIL.

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

Modification 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 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. If an alternative strategy is not proposed, where relevant appropriate warnings that are aimed at preventing potential off-label modifications should be included and explained in the SmPC and PIL.

Any modification of the preparation will change the pharmaceutical characteristics of the preparation as studied in and justified by the clinical trials and (bio)pharmaceutical studies. Therefore it is essential that every modification is verified with respect to its potential impact on the safety and efficacy of the medicinal product. Depending on the type of modification, verification of that modification may include aspects such as patient acceptability, dosing accuracy, compatibility with the proposed vehicle(s) (e.g. in-use stability studies) and the volume or amount to be used, a bioavailability or bioequivalence study comparing the modified and not modified preparation, and any safety risks for the person who will modify the preparation (see section 10).

Bioavailability or bioequivalence studies may not always be required. Existing information from the (adult) development program, established practices, literature data and/or in-vitro studies may provide sufficient justification. Additional information supporting the proposed modification may be provided from clinical trials where the target patient groups have been administered the product according to the alternative strategy and the organoleptic and administration attributes were found acceptable.

Break marks may be used to enable the administration of a fraction of a full tablet dose or to facilitate breaking for ease of swallowing; their intended function should be stated in the SmPC and PIL. The use of break marks in tablets to obtain fractions of the full tablet dose may not be acceptable in all cases due to the criticality of the dose (potent active substances with a narrow therapeutic window). If the use of break marks is recommended in the SmPC and PIL to obtain fractions of the dose, the suitability of subdivision should be demonstrated (including the ease of breaking).

Crushing of a tablet prior to administration may be an alternative strategy for administration to children who have difficulties swallowing an intact tablet. Capsules may be opened and their contents given as such. It may also be an option to disperse or dissolve a tablet or the contents of a capsule in a liquid prior to intake. Taking a part of such a liquid in order to adjust the dose is normally not acceptable, and would require further verification on the ease of preparing the liquid, the homogeneity of the resulting liquid and the ease of measuring the correct volume.

Subdivided or crushed tablets, or the contents of a capsule, may be given with food or drinks. The suitability of the modification(s), including the compatibility with any proposed vehicle, should be demonstrated (see Section 10).

Where the active substance or dosage form characteristics prevent any modification (e.g. toxic active substance, modified release dosage form), 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, 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 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).

Where incorrect dosing is likely to result in a potential serious risk to the health of 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 allows for 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 required to reduce the risk of insufficient shaking and dosing errors due to inhomogeneous distribution of the active substance.

The risks of under- and overdosing to the child as a result of inadequate shaking should be discussed. Clear instructions on correctly withdrawing the dose from the container 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 the 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

Effervescent, soluble and dispersible preparations are intended to be dissolved or dispersed in liquids prior to administration. The suitability 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 required 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 with 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 on whether 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 other suitable 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 medicinal product 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. The patient acceptability should also be discussed in relation to the palatability and sensation of the medicinal product on administration.

For nasal preparations with a local action, the risks of systemic (adverse) effects should be discussed. Devices for nasal administration, along with the intended delivered volume, should be suitable for the size of the nostrils/nasal cavity of 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 used by older children because it is the child who activates the device by inhalation.

6.5. Rectal preparations

Suppositories

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

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 paediatric preparations.

The use of excipients known to sensitize the skin (e.g. some surfactants and adhesives) should be carefully considered and justified. The need for or restriction from using water-impermeable or other types of materials as a coating to the cutaneous medicine should be clarified. Where relevant, the impact of occlusion, fever or thermal heating on skin permeability of the medicine and the consequent 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 prevent the child from removing the patch or medicated plaster. If sites reachable by the child are to be used, the impact of deliberate removal of the patch or medicated plaster on the clinical outcome should be discussed.

Patches and medicated 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 by cutting. Cutting will only be considered acceptable if clearly marked cutting lines are present and if the dose uniformity and consistency of delivery properties have been appropriately demonstrated.

Information on whether the patch can, or cannot be cut to provide a smaller dose needs to be included in the product information, with clear instructions on how lower doses can be obtained by cutting along marked lines. Instructions should also be provided for safely discarding the patch, and regarding 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 the absence of better alternatives, they should be considered acceptable dosage forms for children of all ages.

In order to avoid the use of preservatives with a 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. This is especially important for neonates or 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 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 of 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. The age and weight of the child, the maximum number of injections per day and the duration per treatment should also be discussed. Where appropriate, the use of micro-needles or needle free injectors could be considered, especially for medicines requiring frequent or long treatment period.

The need for serial dilutions to achieve the required dose is 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 preparation 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 be described in the dossier. The volume should be justified according to the age of the children in the target age group(s). Normally, subcutaneous and intramuscular injection volumes should not exceed 1 ml, however lower volumes are warranted for neonates and infants. 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 commonly used in such situations for use by the intra osseous route of administration should be discussed and relevant information should be provided in the SmPC and PIL.

Neonates may only accept very small volumes of medicines in order to avoid volume overload and to allow sufficient room for essential fluid nutrition. Infusions must not be so concentrated that the appropriate dosing rates are not feasible by using standard pump equipment. These aspects should be considered during pharmaceutical development of all parenteral preparations intended for neonates, and in particular of those intended to be administered as a continuous infusion. In addition, specific concerns related to the incompatibility of the medicinal product with other co-administered medicinal products 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.

Out-patient use

In cases where parenteral administration is required for children in out-patient settings, it should be demonstrated that the parenteral preparation 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 applicant should make efforts to consider all possible options for developing an age-appropriate fixed dose combination for all or some target age group(s), 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, the convenience and therapeutic adherence of the child or caregiver. Taking these criteria into consideration, a maximum of 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 medicines should be considered for children where 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).

The use of prolonged release formulations can significantly reduce the dosing frequency and can be beneficial for compliance. Therefore these formulations can be useful for children who would otherwise need to take medication while at school or during the night.

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 preparation should be discussed and it should not result in a serious risk to the health of the child.

In the development of oral modified-release preparations for paediatric use, special attention should be given to the physiological conditions related to the age of the child, 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 suitable excipients in a paediatric medicinal product is one of the key elements of its pharmaceutical development.

Although the basic considerations regarding the use of a specific excipient are similar for adult and paediatric preparations, the inclusion of any excipient in paediatric preparations, even those which are normally accepted for use in medicines for adults or those which are present in authorised paediatric

medicines, requires special safety considerations. The intake of an excipient may result in a different exposure in children to that in adults, or in children of different ages. Also the excipient may have a different effect on developing organ systems. A conservative approach should be followed in case of limited safety data relevant to the use of an excipient in a specific age group.

Overall, the following aspects are to be considered when selecting an appropriate excipient for inclusion in a paediatric medicinal product:

- 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 preparation);
- 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 acceptability including palatability (e.g. local pain, taste);
- 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. A comprehensive development rationale should be provided, taking into consideration the relative benefits and the 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, applicants are recommended to avoid excipients with a potential cause for concern in newly developed paediatric medicines until further research allows scientifically justified conclusions on safety of these excipients to be drawn.

While 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 product is used on a larger scale. Therefore, the added value of the novel excipient in a specific paediatric medicinal product must be well balanced against the use of other excipients with an established safety profile, other dosage forms or other routes of administration.

Allergies can arise in 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 a known potential to cause sensitization or 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:

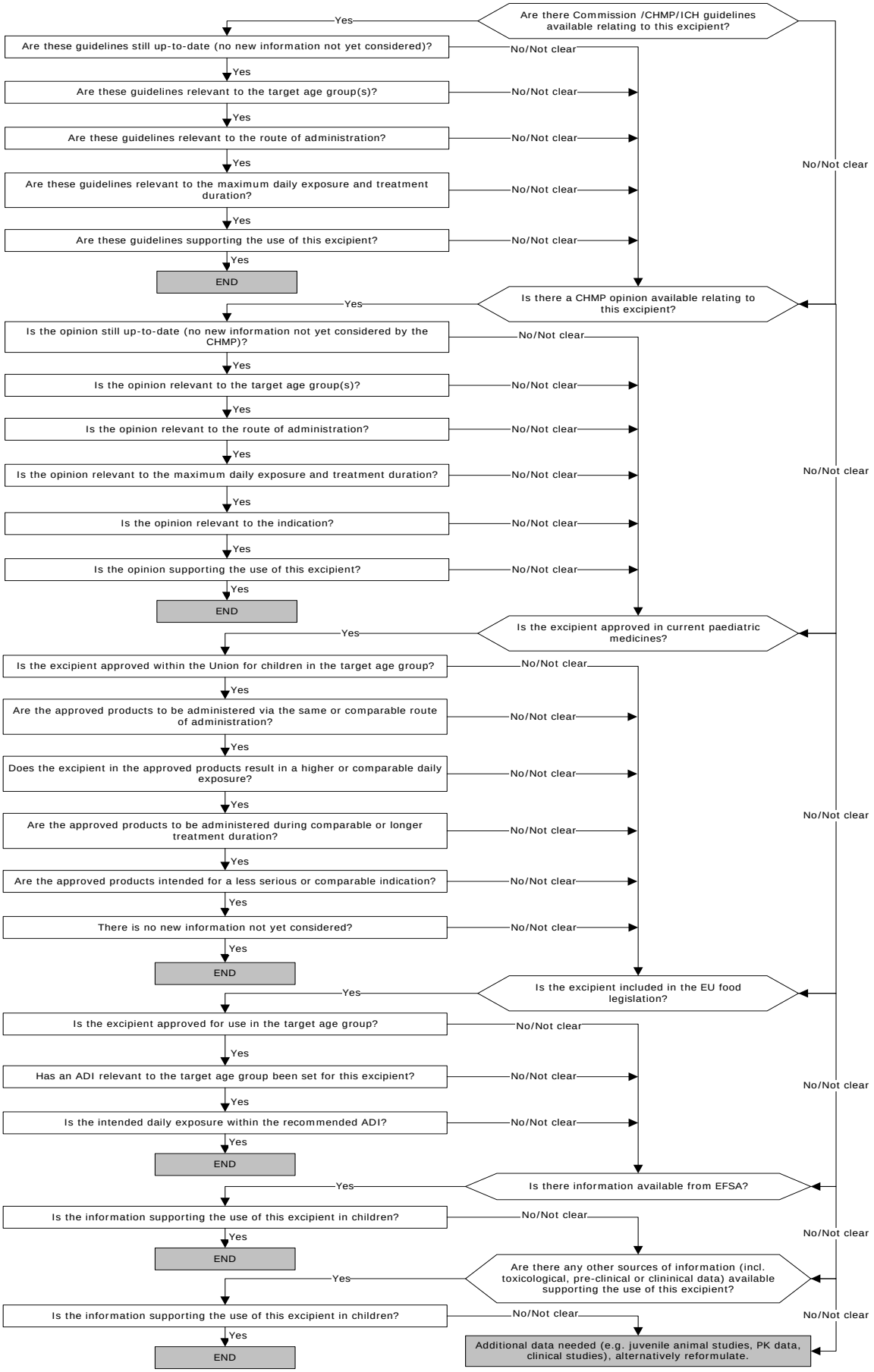
- Commission, ICH and EMA guidelines;
- CHMP scientific opinions (e.g. CHMP position paper, CHMP opinion on a referral procedure);

- 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 the acquired data for the excipient in the proposed paediatric preparation should be summarised and discussed in relation to the target age group(s), 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 a paediatric preparation is safe for its intended use in the 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)

9.2. Colouring agents

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

9.3. Flavours

Adequate palatability plays an important role in patient acceptability, especially in oral liquid formulations, and flavours may be necessary to achieve this goal. The rationale for the use of a particular flavour in a paediatric preparation 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 of different ages. The need to preserve a paediatric preparation and the choice of the preservative system at the lowest concentration feasible should be justified in terms of benefit-risk balance.

The appropriateness of the preservative system for the target age group(s) should be discussed. Unless safety data relevant to children are available, applicants should justify the level of exposure (proposed safety margins) taking into consideration thresholds for adults and 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 acceptability of oral paediatric preparations is paramount and sweetness plays an important role in this.

The choice and concentration of sweetening agents depends on the properties of the active substance and the use of flavours. The rationale for the use of a particular sweetening agent in a paediatric preparation 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).

Frequent and/or high doses of sweetening agents should preferably be avoided in paediatric formulations intended for long term use. The use of cariogenic sugars should be carefully justified. The potential laxative effect of polyols (e.g. sorbitol, mannitol) should be considered, along with their osmotic properties and their potential effects on bioavailability. It should be noted that limited data are available on the relevant thresholds for polyols in children.

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

10. Patient acceptability

Patient acceptability is likely to have a significant impact on patient adherence and consequently, on the safety and efficacy of a medicinal product. Acceptability is determined by the characteristics of the product and the user. The product aspects relate to pharmaceutical characteristics such as:

- palatability, swallowability (e.g. size, shape, texture);
- appearance (e.g. colour, shape, embossing);
- complexity of the modification 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 and duration of treatment;
- 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 preparation should be an integral part of the pharmaceutical and clinical development. Patient acceptability of a preparation should preferably be studied in children themselves as part of a clinical study involving the proposed medicinal product. In justified cases where no clinical studies will be conducted in children or where patient acceptability will not be studied as part of the paediatric clinical studies, adequate patient acceptability of the medicine(s) as proposed for marketing should be demonstrated by other means e.g. by literature references or by studies in dedicated adult panels.

For authorised medicinal products for which the acceptability of the preparation was tested and confirmed during the development or established by market experience, adequate patient acceptability should also be assured during the life-cycle of the product. In case of variation(s), which may have an effect on patient acceptability, e.g. changes to the composition of the authorised formulation, changes to the packaging or user instructions, etc. the impact of the change should be discussed and studied where appropriate and adequate patient acceptability should be reconfirmed.

Adequate patient acceptability is not to be understood as 100% acceptability of a medicine by children in the target age group(s). Moreover, different methods have been described in literature, which resulted in different outcomes when testing the same medicine in the same patient population. As knowledge on acceptability testing is still fragmented and an internationally harmonized method has not yet been developed, the choice of the method and the acceptance criteria are left to the applicant. 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.

Palatability

Palatability is one of the main elements of the patient acceptability of an oral paediatric medicinal product. It may also be an aspect related to the use of a product for nasal administration or inhalation. Palatability is defined as the overall appreciation of an (often oral) medicinal product in relation to its smell, taste, aftertaste and texture (i.e. feeling in the mouth). It is determined by the characteristics of the active substance, the way the active substance is formulated into a finished medicinal product and by the characteristics of the excipients. 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 or literature. The palatability of an 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 preparation should be satisfactory on its own merit, i.e. without mixing with food or drinks.

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

Examples of measures that can be undertaken to improve the palatability of a paediatric preparation include a judicious choice of excipients (including taste maskers, sweeteners and flavouring agents), a change in particle size of the active substance or the excipients, a 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 the free active ingredient in solution by the choice of a different strength and associated change in volume. However, paediatric preparations must not become too attractive to children (candy like) as this is known to increase the rate of accidental poisoning.

Mixing with food or drinks

For a variety of reasons, it may be desirable to give a paediatric medicine with food or drinks. Mixing with food or drinks may either be intended to mask the unsatisfactory palatability of a formulation in cases where it has been demonstrated that it cannot be further improved or where alternative dosage forms cannot be developed. Mixing can also be applied as a further means to improve the patient acceptability including the ease of swallowing of an otherwise already palatable medicinal product. Whatever the reason, the rationale should be discussed and justified in the dossier, and relevant information included in the SmPC and PIL.

The absence of recommendations on mixing with food or drinks will not assure that caregivers will not employ this method in order to administer a medicinal product. Therefore, the effect of mixing the product with common food or drinks as specified by the applicant should be discussed for every oral paediatric medicinal product.

Different food or drinks may have different properties and differ in their effect on the paediatric preparation. The applicant's choice of food or drink should be justified in terms of their actual effects on the properties of the preparation (e.g. acceptability, compatibility and stability). It is understood that food and drinks are usually not standardized products and that the whole range of variability cannot be verified by e.g. acceptability and compatibility studies. Nevertheless, the SmPC and PIL should give clear instructions on what food and/or drinks, if any, have been demonstrated to be appropriate for mixing with the paediatric preparation. If mixing with food or drinks has been evaluated and found to be unsuitable, appropriate warnings should be provided in the SmPC and PIL,

along with an explanation of the basis for such warning. If mixing with food or drinks has not been studied, this should also be stated in the SmPC and PIL. In all cases it should be stated that any mixing outside the recommendations is the responsibility of the health care professional or the user.

The user should be instructed that, in order to facilitate administration of the whole dose, 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 a clearly specified time period after mixing. In exceptional cases a larger quantity may be necessary to assure adequate palatability or dissolution. Large amounts of food or drinks (e.g. one full cup, glass or meal) should be avoided because of the risk that the child may not be able or willing to take the full quantity and consequently will not receive the full intended dose of the medicine. If chewing of the product is expected to affect the acceptability and/or product performance, the SmPC and PIL should clearly state that chewing after mixing with food or drinks must be avoided.

Unless otherwise justified, compatibility should be demonstrated by appropriate studies. The time period during which the mixed product remains acceptable, should be indicated in the SmPC and PIL including information on any restrictions on the temperature of the food or drinks.

Mixing with food or drinks may affect the product performance and the pharmacokinetic behaviour. When mixing with food and/or drinks is proposed, the possible effect on biopharmaceutical characteristics of the medicinal product should be discussed. Assessment of the impact on bioavailability of products mixed with food or drinks may be needed depending on information that is available from studies undertaken during the development of the product, including studies in adults, if relevant to the paediatric medicine.

If the product has been administered following mixing with food or drinks in the clinical trials, no further evaluation may be needed. Mixing with food or drinks is generally discouraged for medicines containing substances with a narrow therapeutic window.

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 medicine.

Unless otherwise justified, container closure systems for use 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.

Applicants are encouraged to consider novel packaging and administration strategies that improve child acceptability, child adherence and child caregiver convenience while 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 medicines 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 successfully remove the entire contents of the container.

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 a paediatric medicine. In these cases it should be demonstrated that accurate 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 device(s) to be employed.

The age appropriateness of an administration device should be discussed. For example, 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 multiple strengths 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 medicine, 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 the accidental use of measuring 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. Therefore this issue needs to be discussed. It should be demonstrated that the dead space is insignificant to the dosing accuracy when the minimum 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 the health of the child 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.

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 package leaflet)

Applicants should provide clear user instructions that favour the correct and full administration of a paediatric medicine. 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, whose pharmaceutical design makes it suitable for use in the target age group(s).

Modification

All activities prior to administration that are undertaken in order to provide the medicine to the patient using an alternative strategy (e.g. in order to improve patient acceptability or adjust the dose). Information on verified modifications (approved by the regulatory authority) should be described in the SmPC and PIL. Non-verified modifications if undertaken off-label are under full responsibility of the health care professional or the user.

Paediatric formulation

The composition of a particular dosage form of a medicine for paediatric use.

Paediatric medicine / paediatric medicinal product

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

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).

Patient acceptability

The overall ability and willingness of the patient to use and its care giver to administer the medicine as intended.

Pharmaceutical design of a medicine

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

Pharmaceutical development

In the context of this guideline, pharmaceutical development relates to all aspects 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 medicine 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.

Preliminary preparation (as called enabling preparation)

A 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 medicine.

Verification (of a modification)

A process of providing any type of adequate evidence, e.g. new (bio)analytical data, from the literature or by referencing to existing practices to support that the proposed modification will not change the pharmaceutical characteristics of the original preparation in a way that it will negatively impact the safety and/or efficacy of the medicine.