EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 May 2011
EMA/CHMP/QWP/180157/2011
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Pharmaceutical Development of Medicines for Paediatric Use

Draft

Draft Agreed by QWP	February 2011
Draft agreed by SWP	March 2011
Adoption by CHMP for release for consultation	May 2011
End of consultation (deadline for comments)	31 December 2011

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

Keywords *child, pharmaceutical development, quality*

Note:

CHMP would like to bring to your attention the three points below for which further input (specific attention) is particularly awaited:

- 6. Route of administration and dosage form
  - 6.2.1: Powders, granules, pellets and tablets:
    - *Acceptability*: tablet size and young children,
    - *Sub-division of tablets*: Use of score lines to administer lower doses
- 9. Excipients in the formulation:
  - 9.1 General considerations: Safety of excipients.

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Executive summary

Children can neither be regarded as small adults nor as a homogeneous group in themselves. As a consequence, paediatric medicines should be appropriately designed for the target age group(s).

In January 2007 Regulation EC No 1901/2006 (the “Paediatric Regulation”) entered into force. As a result of this Regulation, the number of paediatric formulations that the pharmaceutical industry will have to develop to support their clinical trials will increase. It is expected that the number of medicines applying for a marketing authorisation for paediatric use will increase as a result. Therefore, the existing regulatory documents need to be supported by specific regulatory guidance on the pharmaceutical development of medicines for use in children between birth and 18 years of age.

1. Introduction (background)

The physical, metabolic and psychological processes peculiar 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 studies in adults are not necessarily predictive for children. Thus, clinical trials may be needed in children of different ages in order to demonstrate that a medicine is safe and effective in all of the indicated target age group(s).

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, young children are simply unable to swallow conventionally-sized tablets whereas tablets are a favourable dosage form for elder children and adults. Especially neonates pose specific characteristics and needs. They may for example require very small volumes of a parenteral medicine in order to avoid a volume overload. Therefore, children should be treated with medicinal products of which the pharmaceutical design is tailored for use in the target age group i.e. age appropriate medicines.

Knowledge on the critical to quality aspects of paediatric medicines is still limited, especially when considering these aspects in a multidimensional approach to the best attainable and affordable paediatric medicinal products. As a consequence, the usefulness (practicality) of some of the currently paediatric medicines might be questionable / based on minimum standards and could consequently be subject to further optimisation in the interest of parents, other caregivers and children.

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 this Regulation, both the number of paediatric formulations that should be developed by the pharmaceutical industry and the knowledge on the critical to quality aspects of paediatric medicines is expected to increase rapidly.

Bearing the aforementioned in mind, the current regulatory documents need to be supported with guidance on the pharmaceutical development of paediatric medicines. Therefore, this guideline aims to provide additional tools for the rationale pharmaceutical development of medicines for children between birth and 18 years of age to those already described in the current CHMP and ICH guidelines. The 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 medicines that are better tailored for use in children than the

currently authorised, but “questionable” paediatric medicines or the currently applied off-label or pharmacy compounded medicines. The outcome of this balanced approach should not necessarily result in a “gold standard” paediatric medicine.

2. Scope

The principles of this guideline are to be applied during the pharmaceutical development of all paediatric medicines as proposed in Marketing Authorisation Applications (MAA) or applications to extend or vary the marketing authorisation to the paediatric population (MAVs).

As clinical evidence and pharmaceutical knowledge increase over time, 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. If the company is not yet able to propose a paediatric medicine, at least the considerations for the choice of the route(s) of administration, dosage form(s) and excipients in the formulation and administration devices should be discussed, including palatability. The use of preliminary (also called enabling) paediatric formulations in the early clinical trials may be considered acceptable if appropriately justified, however it is not exempting from the requirement to develop a formulation which will be industrially-manufactured and controlled. Thus, preliminary formulations which are based on instructions for the manipulation of an authorised medicine will normally not be considered acceptable for marketing authorisation. A switch from a preliminary formulation to a commercial formulation should be supported by relevant bridging studies between different formulations used throughout the development, including bioequivalence studies if necessary.

Paediatric medicines should comply with all the relevant provisions in the European Union. Therefore this guideline should be read in close conjunction with all the relevant Commission, ICH and CHMP guidelines. However, the current quality provisions of existing guidelines may require further justification or adaptation in view of the specific needs of children. This guideline intends to provide guidance on such adaptation or justification. As a consequence, this guideline will not describe any aspects of the pharmaceutical development of a paediatric medicine that equally applies to medicines for adult use.

Pharmaceutical companies should have a re-evaluation of all their products on the market. They should ensure that their products are state of the art i.e. meeting the requirements as described in this guideline within a period of 5 years following the date of coming into operation of this guideline.

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.

3. Legal basis

This guideline should be read in conjunction with Directive 2001/83 of the European Parliament on the community code relation to medicinal products for human use as amended (further referred to as the Medicines Directive), 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 (e.g. on the establishment of the EMA), and the relevant commission, ICH and CHMP documents with a special emphasize on:

- Ethical Considerations For Clinical Trials On Medicinal Products Conducted With The Paediatric Population – Recommendations Of The Ad Hoc Group For The Development Of Implementing Guidelines For Directive 2001/20/EC Relating To Good Clinical Practice In The Conduct Of Clinical Trials On Medicinal Products For Human Use (2008, Eudralex Vol. 10 Chapter V)
- Excipients In The Label And Package Leaflet Of Medicinal Products For Human Use (Eudralex 3BC7A)
- ICH Q8(R2) On Pharmaceutical Development (EMEA/CHMP/167068 /2004-ICH Q8 R2)
- ICH E11 Clinical Investigation Of Medicinal Products In The Paediatric Population (CPMP/ICH/2711/99)
- Excipients In The Dossier For Application For Marketing Authorisation Of A Medicinal Product (CHMP/QWP/396951/06)
- Guideline On The Role Of Pharmacokinetics In The Development Of Medicinal Products In The Paediatric Population (CHMP/EWP/147013/04)
- Guidelines On Conduct Of Pharmacovigilance For Medicines Used By The Paediatric Population (EMEA/CHMP/Phvwp/235910/2005- Rev.1)
- Guideline On The Investigation Of Medicinal Products In The Term And Preterm Neonate (EMEA/536810/08)
- Guideline On The Summary Of Product Characteristics September 2009, Revision 2
- Guideline On The Pharmaceutical Quality Of Inhalation And Nasal Products (EMEA/CHMP/QWP/49313/2005 Corr)
- Reflection Paper On Formulations Of Choice For The Paediatric Population (EMEA/196218/05)
- European Commission Guideline Entitled 'Guideline On The Format And Content Of Applications For Agreement Or Modification Of A Paediatric Investigation Plan And Requests For Waivers Or Deferrals And Concerning The Operation Of The Compliance Check And On Criteria For Assessing Significant Studies' (Commission Communication 2008/C 243/01).
- CHMP Scientific Article 5(3) Opinion On The Potential Risks Of Carcinogens, Mutagens And Substances Toxic To Reproduction When These Substances Are Used As Excipients Of Medicinal Products For Human Use

4. General considerations

The pharmaceutical design of a medicinal product relates to all aspects as described in Module 3.2.P., the SmPC section 1-3 and 6.0 and the corresponding parts of the PIL, e.g. the composition of the product, the choice of the dosage form, the selected primary and secondary packaging etc.

All aspects of the pharmaceutical design of a medicinal product should be justified, where relevant also in relation to the indicated target age groups. Depending on the aspects to be studied, the ICH classification groups for age may either be divided in smaller groups or combined.

In deciding on the appropriateness of the pharmaceutical design of a paediatric medicine, the focus of attention should normally be placed on:

- the minimum age of the target age group(s) and the relevant developmental physiology;
- the behavioural age characteristics of children in the target age group(s);

- the age associated activities of children in the target age group(s) (e.g. school, nursery);
- the environment where the product is to be used (e.g. hospital or community);
- the condition to be treated;
- the condition related characteristics of the child (e.g. likely disabled, aggressive, fluid restriction, high degree of co-medication including inability to swallow due to centrally nervous system diseases (e.g. epilepsy) or to critical illnesses);
- the 'criticality' of the dose (i.e. steep dose/pharmacodynamic response curve, narrow therapeutic window) and how the dose is to be calculated;
- the maximum duration of therapy which can be foreseen;
- the availability of relevant safety data for the active substance, excipients and the finished medicinal product;
- the pharmaceutical properties of the drug substance (e.g. solubility, taste);
- patient acceptability i.e. child friendliness.

On this basis, the most sensitive development aspects are likely to arise in paediatric medicines for long term use in neonates, infants and young children, particularly when the excipients used are known to have their own undesirable properties, or when the safety data relevant to the target age group(s) may not be as comprehensive as in adults.

5. Characteristics of the active substance

The characteristics of a particular active moiety may be desirably modified by the choice in which the active moiety is manufactured into the paediatric medicine as the active substance. For example the manufacture of a liquid medicine may require a substance with improved solubility i.e. 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, e.g. the base instead of the salt. Moreover, patient safety in children may be improved by avoiding a particular inorganic counter-ion or organic salt structure.

Therefore, the choice of the form of the active substance in the paediatric medicine should be based on its use in the indicated target age group. The selected form may differ from the forms that are employed for the other target age groups or for adults.

6. Route of administration and dosage form

6.1. General considerations

The advantages and disadvantages associated with the administration of a particular paediatric dosage form via a particular route of administration should be discussed and justified for children in each of the indicated target age groups and, where applicable, of different health conditions. Different routes of administration and/or dosage forms may be needed for the same active substance in order to allow adequate treatment of children in all the indicated target age groups, and with a different health condition or disease development.

The justification for the choice of the route of administration and dosage form should include user aspects as e.g. adequate palatability, tablet size etc. The advantages and disadvantages of a particular route of administration and dosage form should also be considered taking account of their inherent consequences for the other pharmaceutical aspects. For example, the choice for a liquid formulation

normally requires a dosing device and preservation unless the company has adopted other measures to guarantee adequate microbiological quality. For example, the choice for an inhalation medicine will require a dedicated medical device.

6.2. Oral administration

Oral administration can be achieved via several types of dosage forms. In general, the main choice is between the application of an oral liquid preparation, an oral solid unit dosage form (e.g. normal sized tablet, capsule) or an oral flexible solid dosage form (e.g. powder, granules, pellets).

Children may be unable to swallow solid unit dosage forms. Oral solid unit dosage forms will also result in a decreased dosing flexibility as compared to oral liquid preparations and oral flexible solid dosage forms. This may be a problem in case dosing is weight dependent. Both disadvantages can be overcome by the application of an oral liquid preparation or an oral solid flexible dosage form. However, the application of a large range of doses with an oral solid flexible dosage form may necessitate the need for a dedicated device in order to avoid dosing errors. Solid oral dispersible tablets will also enable dosing flexibility, if parts of the dispersed solution are taken. However, correct dosing will then require a fully dissolved solution or a homogeneous dispersion, the correct volume of water to be added and the correct volume of the dissolved solution or dispersion to be taken. Such handling is prone to errors and normally not considered acceptable.

Oral administration will usually occur via normal swallowing and drinking, however, feeding tubes may be applied where relevant, see 4.3.9.

6.2.1. Powders, granules, pellets and tablets

Acceptability

Powders, granules and pellets may be given to children from birth when administered as a solution. If appropriately justified, the application of a liquid dispersion may be acceptable from birth as well.

If powders, granules or pellets are administered in their solid form, they will normally be considered acceptable from the moment the infant is able to accept solid food. This is usually around six months age. The risk of aspiration, choking and where relevant chewing should be considered depending on the target age group, size, shape, quantity (volume) and the type of the active substance and dosage form (e.g. gastro-resistant and modified release).

The tablet size is fundamental to the ability of a child to swallow a tablet. Young children may be able to accept small tablets, but not large tablets. Unless otherwise justified by appropriate studies or clinical evidence, small tablets (i.e. tablets from 3 to 5 mm diameter, width or length whichever is the longest) will not be considered acceptable for children below the age of 2 years, medium sized tablets (i.e. tablets from 5 to 10 mm) for children below the age 6 years; large tablets (i.e. tablets from 10 to 15 mm) for children below the age of 12 years and very large tablets (i.e. tablets from 15 mm) for children below the age of 18 years.

For chronic diseases, tablet size acceptability in children may be improved by adequate training techniques. Such training may allow a larger size for age groups than normally considered acceptable. Tablet size acceptability may also be improved by adequate instructions for joint intake with semi solid food. In order to avoid a wide range of strengths, a single dose may normally involve several small sized tablets.

The suitability of tablets in children should be further justified in relation to the disease and the risks associated to under-dosing, choking and aspiration. Any identified risks should be carefully balanced against the risks associated with the application of an alternative dosage form.

Appearance

Overly attractive oral solid dosage forms should be avoided. Every effort to differentiate the appearance of tablets from confectionary should be made.

Sub-division of tablets

It is highly likely that every line on a paediatric tablet will be used in daily practise as a scoring line to lower the dose, either within or off-label. Therefore, every line on a tablet for paediatric use should result in equal tablet parts according to the criteria of the Ph. Eur. monograph on sub-division of tablets. Thus, it is not considered sufficient to state in the SmPC and PIL that the scoring line is only meant to facilitate the administration of both halves at the same time and not to divide the tablet in two halves.

Crushing tablets

Unless otherwise justified, crushing of a tablet prior to administration should not be the standard procedure to treat children in the indicated target age groups. Any justification should at least include:

- the possibility to market the (tablet) granules in a single dose sachet or a capsule that should be opened prior to use;
- the impact of crushing on palatability;
- patient acceptance;
- bio-availability and
- the risk for the person who should be crushing the tablets.

Dispersible tablets

The minimum volume for dispersion should be described and justified in relation to the indicated target age group(s). For well palatable solutions, the volume should not exceed 20 ml including any rinsing where relevant for children below the age of 4, and 50 ml including any rinsing where relevant for children from 4 years. The minimum volume for dispersion should also be stated in the SmPC and PIL.

Parents may wish to administer dispersible tablets by other means as intended i.e. as a normal tablet without any prior dispersion. At the same time, children may not directly swallow any given tablet, but decide to keep the tablet in their mouth for a period of time thereby using it as an orodispersible tablet. The impact of these two alternative administration methods on the safety and efficacy of the medicine should be discussed. The issue should be clarified to the users in the SmPC and PIL.

Orodispersible tablets

Children may take orodispersible tablets by other means than intended i.e. the tablets may be swallowed without dispersion in the mouth. Caregivers may also wish to disperse the medicine in a liquid prior to giving it to the child because they are afraid that the child will swallow the intact medicine. The impact of those two alternative means on the safety and efficacy of the medicine should be discussed. The SmPC and PIL should clarify whether or not the orodispersible tablet may be used as a dispersible tablet. The direct swallowing of an orodispersible tablet without prior dispersion in the mouth should not result in relevant safety and efficacy problems.

6.2.2. Capsules

Hard and soft capsules may be taken intact. They may also be opened and their contents taken as such. The suitability of both approaches should be discussed and justified for all the indicated target age group(s).

If a hard capsule is to be opened prior to use, its contents should meet the same requirements as stated for powders, pellets or granules where relevant. If a soft capsule is to be opened prior to use, its contents should meet the same requirements as oral liquid preparations where relevant. Instructions for removal of small amounts of liquid from a soft capsule and then subsequently administration by the oral route can result in dosing errors and this approach is normally not considered acceptable.

Only if capsules are to be taken intact, the dimensions of the capsule should be justified in relation to the target age group(s), child health conditions, inter patient differences and the risks associated to accidental choking or chewing. Normally, the smaller hard capsules are only considered acceptable from the age of 6 years if to be taken intact.

6.2.3. Oral liquid preparations

General considerations

Oral liquid dosage forms are normally considered acceptable for children from full term birth.

Oral multi-dose liquid dosage forms will normally need to be preserved (see section 9.4), 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. Nevertheless, preserved solutions will generally be considered as an acceptable dosage form for children from birth.

Oral liquid dosage forms for children should be packaged together with an appropriate dosing device. If dosing to the indicated target age groups requires multiple deliveries of the most appropriate strength of the liquid preparation with a device (e.g. when dosing ranges from 0.5 to 15 ml), then preferably multiple devices with a different dosing content should be provided with the packed medicine in order to assure the availability of an appropriate device to the patient (for this example e.g. both a 3 ml device and 15 ml dosing device). Further instructions on the dosing device are provided in section 11.3.

The risks of incorrect or accidental overdosing with the dosing 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 medicine. Adequate measures should be undertaken in cases where incorrect dosing is likely to result in a potential serious risk to public health. Such measures may e.g. involve the application of unit dose packagings as pre-filled oral syringes or cups for single use or the selection of another dosage form.

For oral liquid solutions and dispersions, the maximum recommended single dosing volume is 5 ml for children aged below 4 years and 10 ml for children aged between 4 and 12 years. The minimum dosing volume will be determined by the accuracy of the dosing device.

Oral suspensions

The potential for dosing errors of the minimum and maximum recommended doses in the relevant target age groups should be discussed with regard to sedimentation and sticking of the suspended active substance to the primary container and to the dosing device.

In addition, the risks of under-dosing and over-dosing to the child should be discussed for the worst case scenario i.e. not shaking the container properly or not shaking it at all. Adequate measures should be undertaken in cases where incorrect shaking will result in a potential serious risk to public health. Such measures may involve the application of unit dose packagings as pre-filled oral syringes or cups for single use or the selection of a different dosage form.

Drops

Oral liquid drops can provide a means to administer medicines in low doses or small volumes. 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 solution and the method of dropping. The maximum number of drops per single intake should be stated and should normally not exceed 10 drops (i.e. about 0.5 ml).

The accuracy and precision of the volume dispensed should be justified in relation to the criticality of the dose. Unless otherwise justified, oral liquid drops will only be considered acceptable for medicines with a wide therapeutic window in view of the potential for dosing inaccuracies.

6.2.4. Medicines for oromucosal administration

The size and shape of oromucosal formulations should be considered for each of the target age groups in relation to the local area where they should be applied.

In order to avoid the risk of swallowing mouthwashes or dental gels, these medicines need to be applied using a cotton bud, sponge or similar attribute in younger children.

6.3. Medicines for nasal administration

Nasal medicines will normally be considered suitable for children of all ages. The suitability of the nasal route of administration for local and systemic treatment a particular medicine should be discussed and justified in terms of the likelihood that the active substance (and excipients) will cause pain or irritation. Also, the patient acceptability in view of palatability and sensation of the medicine on actuation should be discussed and justified.

For nasal medicines with a local action, the risks of systemic (adverse) effects due to both correct and incorrect application should be discussed. Devices for nasal administration should be adapted to the size of the nostrils/nasal cavity for the intended target age group(s).

6.4. Orally inhaled (pulmonary) medicines

The patient acceptability and age-appropriateness of orally inhaled 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. Elder children may use the inhaler with or without a spacer .

Dry powder inhalers can usually only be applied by elder children because it is the child patient which makes his or her dose by the inspiratory flow. For high potency medicines, multi-dose containers with a secure dose counting, an end of life lock-out system and measures to prevent inadvertent multiple dosing should be developed in order to reduce the risk of accidental overdosing.

6.5. Rectal administration

Suppositories

The size and shape of the suppository should be tailored to the 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.

Liquid rectal preparations

The length of the canule of the enema and any volume to be administered should be tailored to 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 administration

The skin undergoes many changes from birth into adult hood. These differences should be taken into consideration when developing cutaneous medicines for children.

The use of excipients known to sensitize the skin should be carefully justified. The need or restriction to use water-impermeable materials as a coating to the cutaneous medicine should be stated. Where relevant, the impact of coatings, fever or thermal heating on skin permeability and the risk to 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 should are preferred. If other sites 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 as a single dose/strength. However, especially for children, they may be developed to provide for a range of doses/strengths by cutting. Cutting will only be considered acceptable if cutting lines are present and if dose uniformity and consistency have been appropriately demonstrated.

6.7. Preparations for administration in the eye and ear

Preparations for the ear and the eye are mostly developed for a single patient group, including children, adults and the elderly. Preparations for the ear and the eye 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 (potentially toxic) preservatives in multi dose preparations, 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 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 site of injection, the injection volumes 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, needle free injectors should 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 dosing device. Where relevant, the size of the syringe and the graduation that permits accurate administration should therefore be described as well. For the currently available 1-ml syringes, the smallest volume for parenteral administration is set at 0.1 ml. Unless otherwise justified, subcutaneous and intramuscular injection volumes should not exceed 1 ml.

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. This aspect should be considered when developing parenteral medicines for pre-term and full term neonates, in particular to medicines intended to be administered as a continuous infusion.

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 sufficiently tailored to the 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. Administration through feeding tubes

For oral medicines for which the administration via a feeding tube cannot be regarded as an exception but rather as the rule (e.g. in pre-term neonates), the particle size, viscosity, dosing volume and compatibility of the oral medicine with the tube material should be discussed and justified. Dose recovery after extrusion through the nasogastric tube should be demonstrated using rinse volumes relevant to the target age group. In addition and if relevant depending on the location of the tube, the risks associated to the accidental aspiration of the medicine should be discussed.

The impact of the administration of an oral medicine through a feeding tube on bio-availability should be discussed.

The aforementioned requirements also apply for medicines where the SmPC and PIL state that the medicine may be administered through a feeding tube.

6.10. 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. 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 intended clinical effect (immediate release versus prolonged release) and child patient and caregiver convenience/therapeutic adherence. 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).

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.

8. Modified release preparations

Modified release medicinal products should be considered for children when relevant. Depending on the size of the particles, especially multiparticulate systems may be applicable across a wide age range. 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 (eg. transdermal).

For solid oral modified release preparations, the risk of chewing is likely to affect the suitability of the dosage form. The risk of chewing on the efficacy and safety of the medicine should therefore be discussed and should, unless otherwise justified, not result in a serious risk to public health.

In the development of oral modified-release formulations for paediatric use, special attention must be given to the physiological conditions 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. These aspects should also be considered when designing in vitro testing during pharmaceutical development.

9. Excipients in the formulation

9.1. General considerations

The suitability of an excipient in a paediatric medicine is a key element of the pharmaceutical development process.

Although any basic considerations regarding the use of a specific excipient in a medicinal product will not be different for adult and paediatric medicines, the inclusion of any excipient in a paediatric medicine requires additional concern in view of the potential risk of more pronounced safety implications. Overall, the following aspects are to be considered with respect to the selection of an appropriate excipient:

- the pharmaceutical technologic characteristics of the excipient and potential alternatives;
- the safety profile of the excipient for children all over the indicated target age groups on basis of single and daily exposure (and not the concentration or strength of the medicine);
- the expected duration of treatment i.e. short term versus long term;
- the criticality of the condition to be treated;

- the characteristics of the disease;
- manufacturability;
- allergies and sensitization.

The safety implications of an excipient for a specific target age group and route of administration at the proposed daily intake can range from absent until fully unacceptable and may include all stages in between e.g. low risk, moderate risk etc. Although the final evaluation on the acceptability of the excipient in the medicinal product should be based on an overall risk to benefit evaluation of the product itself, it must be acknowledged that an overall positive risk to benefit assessment is not considered an acceptable argument to market poorly developed medicines. Thus, 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. In other words, applicants should not come with a single fait accompli when excipients with an identified risk are intended to be used. It is expected that a comprehensive development rationale will be provided, taking into account the relative benefits and risks of a number of possible and feasible alternatives. This principle is already established in the Concept Paper for this guideline.

New evidence may suggest that the safety of some excipients that are commonly used in licensed paediatric medicines, may be subject to debate, either as such, above some daily intake or in some target age groups. All this would require further research before a final conclusion can be drawn. Until then, pharmaceutical companies are recommended to avoid questionable excipients in new paediatric medicines.

Whilst it is acknowledged that the use of a new excipient in a paediatric medicine is fundamental to pharmaceutical innovation and whilst it is acknowledged that the use of such a new excipient may be well justified by appropriate pre-clinical studies, it must be realized that safety issues may only become apparent when the medicine is used on a larger scale. Therefore, the added value of the new excipient in a specific paediatric medicine must be well balanced against the use of other excipients with a known safety profile and against the use of other dosage forms or routes of administration that do not require the use of this new excipient. If used, the safety profile of any new excipient should be closely monitored post marketing.

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, pharmaceutical industries are encouraged to develop medicines that do not contain excipients that are known for their potential to cause sensitization/allergies.

The following information sources should be consulted in order to assess the safety profile of an existing excipient in a paediatric medicine (see Figure 1):

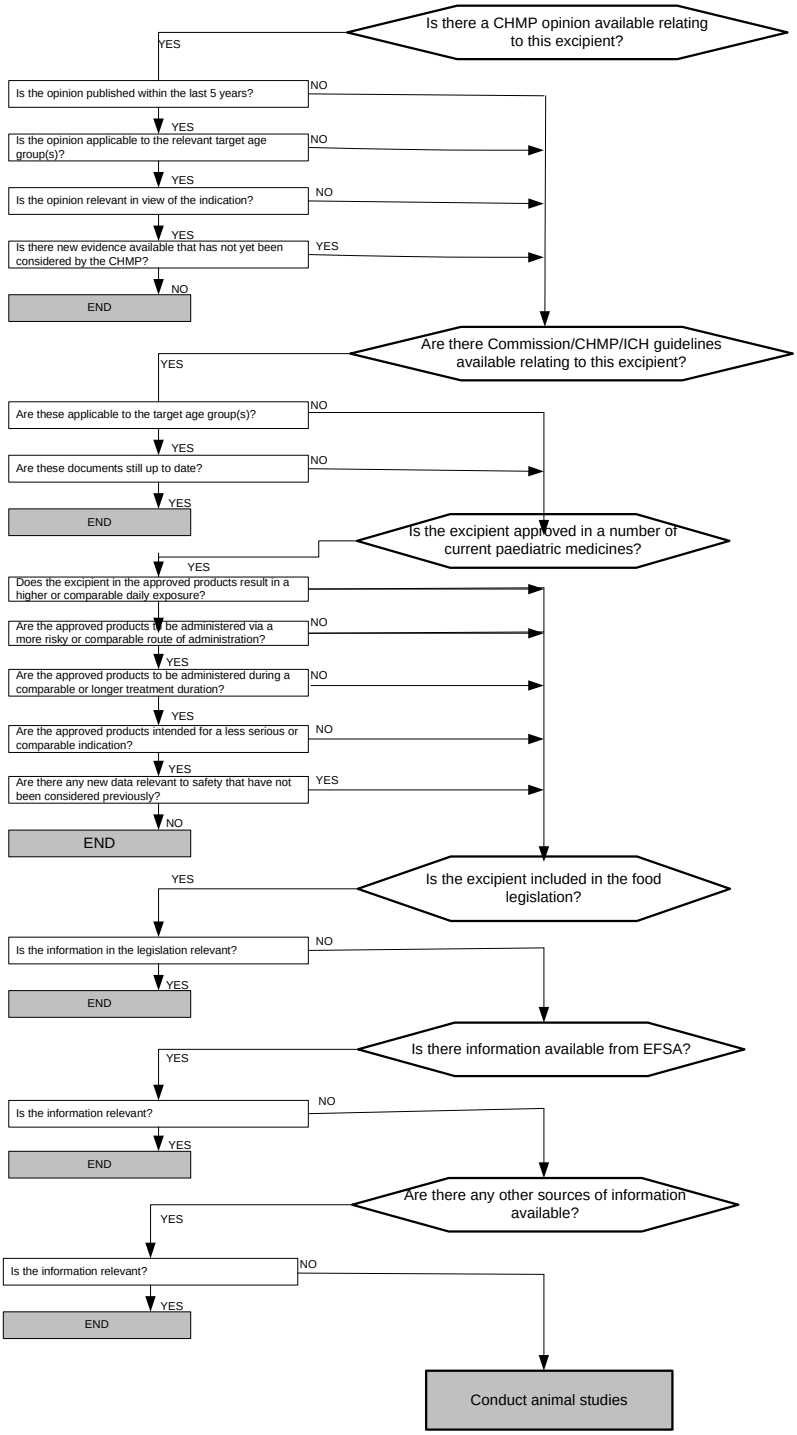
- The Commission, ICH and CHMP guidelines;
- CHMP scientific decisions where applicable and as e.g. reflected in Questions and Answer documents on the EMA website, opinions, referrals etc;
- The excipient composition of currently authorised medicines for children.
    - A reference alone is not sufficient. For each of the relevant target age groups, the indication, route of administration, treatment duration, dosage form, concentration, maximum daily excipient intake and exposure should be taken into consideration in all or a sample of the licensed medicines.

- Food Legislation.
    - This source of information poses some limitations as it relates to food only (i.e. chronic and long term use), the data may not clearly relate to children and the safety margins may be rather wide;
    - All additives, flavours, preservatives and colorants described in the Food Legislation and 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 as acceptable in view of normal dietary routines by the indicated target patients;
    - The aforementioned does not apply to neonates for which further non clinical data is required;
    - The safety of additives, flavours, preservatives and colorants that are described in the Food Legislation requires further evaluation for use in non-oral dosage forms;
    - It should be remembered that parents or caregivers that need to avoid a certain excipient may be able to do so for food, but that there may not be any alternative for a medicine. Therefore, the justification of an excipient in a paediatric medicine by reference to the Food Legislation should be considered in view of known allergies as well. A more strict approach may apply.
- 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 use) and the data may not relate to children. However a warning for adults may question the safety of the excipient for 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.

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 and target age group. New toxicological studies may be necessary if the use of an existing excipient in a paediatric medicine can not be justified on basis of the aforementioned information sources.

As safety information on excipients for use in children is scarce and fragmented, the EMA intends to publish an annex to this guideline providing an oversight of the most current information. However, it must be reminded that this annex can not be used as the sole justification and does not allow applicants to refrain from the aforementioned methodology for justification of the safety of an existing excipient for use in a paediatric formulation.

Figure 1: Decision tree for the evaluation of the safety profile of existing excipients in paediatric formulatios for a specific target age group



end i.e. 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

Colouring agents allowed in foodstuffs are also allowed in medicines. However, foods for infants or young children must not contain added colours except in some specified cases. Patients that wish or need to avoid a certain colouring agent can avoid foods containing that agent, but for a medicine there may not be any alternative. As a consequence, paediatric medicines should normally not be coloured.

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 groups, child patient and caregiver's acceptability and the need to avoid accidental dosing errors. Where there is a need to differentiate between similar medicines 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 medicine and the selection of a particular colouring agent. Azo-dyes are not considered acceptable as better alternatives are commonly available.

In relevant cases the lack of a colouring agent in a paediatric medicine should also be discussed and justified in the light of all measures undertaken to avoid accidental dosing errors.

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 according section 9.1 and 9.5.

The use of flavours should be justified by the company, including the choice of natural versus synthetic flavours. Natural or chemical equivalents of natural flavours should be used if possible. The qualitative and quantitative composition of the flavours should be provided. In addition, safety concerns should be discussed. These concerns should include potential impurities (i.e. residual solvents) and the risk of allergies and sensitization.

9.4. Preservatives

Preservatives have a potential to cause toxicological problems, especially in young 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 risk to benefit balance should at least take account of the facts as described underneath. It is emphasized that the general chapter on excipients also applies to preservatives.

The appropriateness of the preservative system for the indicated target age groups should be discussed. It may become necessary to use more than one preservative in certain circumstances. The individual and combined toxicity of the preservatives should be considered. When the lowest concentration feasible to achieve appropriate microbiological preservation is close to the level that would not be acceptable from a safety prospective, applicants should consider alternative dosage forms.

9.5. Sugar versus sweeteners

The importance of palatability in paediatric formulations is paramount and sweetness plays an important role in this. Sweetness can be achieved by the use of natural or artificial (synthetic) sweeteners. Sweetening agents can be categorised as follows:

- cariogenic sugars (e.g. sucrose, fructose and glucose);
- non-cariogenic sugars (e.g. hydrogenated glucose syrup (maltitol), mannitol, sorbitol, and xylitol);
- synthetic sweetening agents (e.g. aspartame, acesulfame potassium [Ace K], saccharin).

The choice and concentration of sweetening agents may be governed to some extent, or totally, by the properties of the active substance. However, the following considerations should normally also be taken into account when choosing a formulation and justified.

- effect of sugar content on teeth (dental caries);
- dosing frequency of the medicine i.e. once daily or multiple dosing per day;
- duration of use of the medicine i.e. short-term (e.g. antibiotic) or long-term (e.g. anti-epileptics);
- products containing a high percentage of sugar are more or less self-preserving thus eliminating or reducing the need for additional preservative (s);
- side effects of larger daily exposure of especially non cariogenic sugars (diarrhoea);
- artificial sweeteners achieve sweetness in low concentrations;
- the severity of the condition to be treated (e.g. is the risk side effects of secondary concern to adequate patient compliance in view of the risk to benefit balance);
- compatibility with other ingredients;
- any effect of the sweetening agent (s) on the absorption of the medicine in the sick child.

10. Patient Acceptability

Patient acceptance can be defined as the overall ability of the patient to use a 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 medicine such as 1) palatability, size and shape; 2) the required dose e.g. the dosing volume, number of tablets etc.; 3) the required dosing frequency; 4) the selected administration device; 5) the primary and secondary container closure system and 6) the actual mode of administration to the child. For paediatric medicines, the user may comprise both the child and its adult caregiver.

Evaluation of the patient acceptability of a medicine should be an integral part of the pharmaceutical development studies. For medicines falling under the scope of the Paediatric Regulation, patient acceptability of the medicine should preferably be studied in children themselves as part of the clinical trials. In justified cases where no clinical trials will be conducted or in justified cases where patient acceptability will not be studied in the clinical trials, 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. It should be thoroughly investigated if drop outs and poor compliance during the clinical trials are due to a bad patient acceptability.

For medicines that do not fall under the scope of the Paediatric Regulation, adequate patient acceptability is also encouraged to be tested during paediatric clinical trials if any. If not, adequate palatability should be demonstrated otherwise e.g. by data from literature, studies in dedicated adult panels or feedback from patients who have been using the same or a similar product. In lack of actual data in children, applicants are encouraged to confirm the adequate patient acceptability post

marketing by actual studies in children who are already under treatment or by a careful evaluation of voluntary patient feedback.

Palatability is one of the main elements of the patient acceptance of an oral 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) medicine 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, literature or in-vitro measurements such as the electronic tongue. 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 beverages).

The target quality product profile can be tailored at a paediatric medicinal product with a neutral taste or a paediatric medicinal product with a specific and generally acceptable taste. The choice for 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 the intended target palatability (neutral or a specific taste) should be clearly described and include information on relevant alternative compositions or dosage forms.

The measures that can be undertaken to improve the palatability of a medicinal product e.g. involve the selection of the excipients including taste maskers, sweeteners and flavouring agents, a change in the particle size of the active substance or excipients, the choice of a different salt form of the active moiety, coating of the active substance, coating of the finished dosage form, the application of a complexing agent or for liquid preparations by any means to lower the amount of free drug in solution such as the choice of a different strength and subsequent change in volume. Any oral paediatric dosage form should by no means become too attractive to children (candy like) as this is known to increase the rate of accidental poisoning.

Mixing instructions with food or beverages may be recommended in the SmPC and PIL. The instructions can either be intended to mask the unsatisfactory palatability of a medicinal product in cases where it has been demonstrated that the palatability of the medicine cannot be further improved and where it is not an option to select an alternative dosage form. Or mixing recommendations can be applied as a further means to improve the patient acceptability and the ease of swallowing of an otherwise already palatable medicinal product.

In cases where mixing instructions are provided to mask the unsatisfactory taste of a medicinal product, it should be discussed which foods mask the original taste best. The applicant should understand whether the medicinal product is likely to dissolve in the food. The applicant should demonstrate that the medicine becomes sufficiently palatable after mixing with the recommended foods or beverages. The patient should be informed that such mixing is not an option, but a necessity. In all other cases, mixing instructions with food or beverages do not need any further justification from the perspective of patient acceptance.

However, certain foods of beverages may affect the bio-availability and/or therapeutic action of the medicine. Moreover, the lack of recommendations on mixing with food or beverages 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 different types of common food or beverages for children should be discussed and/or studied in the development pharmaceutics targeting at in in-use shelf-life of 30 minutes.

Caregivers should be instructed in the SmPC and PIL that any mixed medicine should be taken immediately i.e. within 5 minutes. Positive mixing instructions with common food or beverages are recommended. Appropriate warnings should be added in cases where the medicine can not be mixed with certain food or beverages for even 5 minutes or shorter.

If possible, the adequate palatability of a medicinal product should be studied as part of the patient acceptability studies. Otherwise, adequate palatability should be demonstrated by other means and confirmed post marketing in real patients. Actual palatability studies may be conducted in several ways. The suitability of the chosen method 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 resistance), and should take account of the characteristics of the target age group, the condition relevant to the medicine, incidental and multiple use, co-medication and differences between countries.

11. Container closure system, dosing device and administration device

11.1. General considerations

The container closure system, dosing device and/or administration device should be tailored for use in children in the indicated target age groups and/or their adult caregivers.

When combined, they should allow the contents to be removed from the container in a way that is appropriate for the intended use of the preparation and that takes account of the need for any administration devices. E.g. the use of an oral syringe will require a dedicated container cap.

Unless otherwise justified, container closure systems for outpatient 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.

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

11.2. Container size

General considerations

The contents of a container should be justified in terms of 1) the dosing recommendations and dosing duration in the SmPC and PIL for each of the indicated target age groups; 2) accidental dosing errors; 3) accidental ingestion of the full container contents, 4) environmental waste and 5) the risk of unapproved multiple usage of a product for single use for reasons of e.g. cost reduction. For liquid preparations for single use, the contents of the container should normally be less than 10-fold of the lowest recommended dose.

Oral medicines

Powders, pellets and granules for oral use should be packed in containers for single use. They can be packed in larger volumes in sachets, but also in smaller volumes in capsules. Alternatively, a dedicated "administration device" can be acceptable.

Parenteral preparations

Where the volume of the paediatric medicine in the container is aimed at a lower age group, in exceptional circumstances, the administration of multiple vial contents by a single injection may be acceptable to the elder age groups. However, the use of more than a single pre-filled syringe to treat a single child is not considered acceptable as this would require multiple injections.

11.3. Dosing device

Specific attention should be given to the ease of administration by the caregiver or the child itself, also with respect to unwilling children.

Oral syringes must not be able to accept needles. Appropriate measures should be undertaken in order to reduce the risk that the cap is accidentally co-administered into the mouth of the child.

The minimum volume that may be administered should be determined based on the accuracy of the device.

Graduations on the dosing device should be based on the relevant dosing recommendations of the medicinal product for children in each of the indicated target age groups. The contents of the dosing device and the graduation on the device should be assessed in view of the risk of over and under dosing and the availability of a higher or lower strength of the medicinal product. In exceptional cases, there may be a need to pack multiple dosing devices with the product in order to allow the health care professional to dispense the appropriate device.

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 multiple use of a dosing device in order to provide a single, recommended dose is normally not considered acceptable e.g. a single 7.5 ml dose should not be given by a 5.0 ml syringe. Dosing devices may be used for repeated dosing, if appropriately cleaned. A cleaning instruction should be included in the SmPC. If a device is specifically designed to deliver the correct doses for a particular product, then the product name should be displayed on the device in order to avoid mixing devices for different medicines.

Spoons and cups are not considered acceptable for liquid preparations with a narrow therapeutic window or volumes below 5 ml. Otherwise, spoons and cups will only be considered acceptable if all of the relevant dosing intervals can be conducted with the device with an acceptable dose accuracy and reproducibility.

11.4. Other devices

For routes of administration requiring the use of a specific administration device, the appropriateness of the device for the indicated target age groups should be justified. This applies especially to devices requiring co-ordination and co-operation. The anatomy and physiology of the site of application should be taken into consideration.

For all inhalation and nasal drug products particular care should be given to the appropriate size of the administration device, the ability of caregivers to administer the product correctly to potentially unwilling children, and the robustness of the device in daily practice. Any necessary device should be dispensed with the product or commercially available.

12. User information (Summary of Product Characteristics and Patient Information leaflet)

Pharmaceutical industries should provide clear user instructions that favour the correct and full administration of the medicine. These instructions should take account of the different administration scenario's to children from birth into adulthood: Where relevant, instructions that are both tailored to 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 and the full chapter 4 of this guideline.

Definitions

Age-appropriate paediatric medicines

Medicines pharmaceutical design of which is tailored for use in the intended age group.

Preliminary formulations (as called enabling formulation)

Preliminary formulations are relatively simple and easy to prepare formulations that facilitate preclinical and early clinical development studies which might otherwise be delayed whilst developing the final appropriate paediatric medicinal product.

Manipulation/ Manipulated authorised medicinal products

The word manipulation is only to be used in relation to an authorised medicinal product. It reflects a deliberately change of the pharmaceutical characteristics of an authorised medicine i.e. all pharmaceutical handlings by the health care professional or patient that are not described in the SmPC. Manipulation can be simple e.g. breaking a tablet with a tablet splitter or re-packing a parenteral solution into a glass container with a screw cap and syringe for oral use. Manipulation can also be rather complex e.g. using a tablet as the source for the active substance for a suspension.

Paediatric formulation

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

Paediatric medicine / medicinal product

The paediatric formulation in its primary and secondary packaging, together with any dosing 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 marketing authorisation dossier, 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. control of raw materials, validation of analytical methods etc.

Pharmaceutical design of a medicinal product

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