Draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use

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Background (1)

Children can not be regarded as small adults

- On the 26th January 2007 the Paediatric Regulation entered into force
- This regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population

Background (2)

Intention of this Regulation:

- Number of paediatric formulations should increase
- The knowledge to quality aspects of paediatric medicines is expected to increase rapidly
- Improvement of availability of information on the use of medicinal product in various paediatric populations

Background (3)

Guideline should be read in conjunction to

- Directive 2001/83 of the European Parliament on the community code relation to medicinal products for human use
- Directive Regulation 1901/2006/EC of the European Parliament and of the Council on medicinal products for paediatric use
- European Pharmacopoeia

Pharmaceutical Problems (1)

Problems:

- Young children are unable to swallow conventionally-sized tablets
- However, tablets are favourable dosage forms for elder children
- Neonates pose specific characteristics and needs

Pharmaceutical Problems (2)

Problems:

- Neonates require very small volumes of a parenteral medicine in order to avoid a volume overload
- The taste of medicine for young children (bitter taste of some active substances)
- Ecipients with highly allergic potential, however are unavoidable
- Preservatives

Pharmaceutical Problems (3)

Problems:

- Incompatibility of the active substance with food/beverages
- Container Closure System: Young children should not be able to open medicines
- Dedicated medical devices (inhalation medicines)
- Knowledge on the critical to quality aspects of paediatric medicines is still limited

Scope (1)

Scope:

- The principles of this Guideline are to be applied during pharmaceutical development or
- Applications to extend or vary the marketing authorisation to the paediatric population

Scope (2)

Scope:

- Re-evaluation of products on the market are necessary
- It should be ensured that the products are state of the art, i.e. Meeting the requirements within a period of 5 years (date of coming into operation of this guideline)

Characteristics of the Active Substance (1)

Active Substance

- Choice of the form should be based on its use in the indicated target age group
- Liquid medicines may require a substance with improved solubility (different salt or a salt instead of the base
- Child acceptability may be favoured by selection of a less soluble form (base instead of the salt)
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Characteristics of the Active Substance (2)

Active Substance

Patient safety!

- Avoiding particular inorganic counter ion or organic structure

Dosage Form

General considerations:

- Administration route should be discussed and justified in each indicated target age group
- Adequate palatability
- Tablet size
- Advantage/Disadvantage of a particular route of administration and dosage form should be discussed
- Liquid formulations require a dosing device and preservation
- Inhalation medicines require a dedicated medical device

Oral administration (1)

Acceptability:

– From the moment when infants are able to accept solid food (six months age)

- Risk of aspiration, chocking and where relevant chewing should be taken under consideration with focus on the target age group
- Risk of under-dosing

Oral administration (2)

Tablet size:

- Small tablets (3 to 5 mm diameter) are not acceptable for children below the age of 2
- Medium size tablets (5 to 10 mm diameter) are not acceptable for children below the age of 6 years
- Large Tablets (10 to 15 mm diameter) are not acceptable for children below the age of 12 years
- Very large tablets (15 mm and more) are not acceptable for children below the age of 18 years

Oral administration (3)

Appearance:

- Overly attractive oral solid dosage forms should be avoided
- However, efforts to differentiate the appearance of tablets from confectionary should be made

Sub- division:

- Every line on a tablet should result in equal parts according to the criteria of the Ph.Eur. Monograph
- Not sufficient to state that the scoring line is only meant to facilitate the administration

Oral administration (4)

Crushing tablets should be justified in the light of:

- Possibility to market granules/capsules/single dose sachet opened prior to use
- Impact of crushing on palatability
- Patient acceptance
- Bio-availability
- Risk for the person who should be crushing the tablets

Oral administration (5)

Capsules

- Hard capsules opened prior use- contents should meet the same requirements as stated for powders/granules
- Soft capsules opened prior use – contents should meet the same requirements as oral liquid preparations
- Instructions for removal of small amounts from the soft capsule are necessary as it may result in dosing errors

Oral administration (6)

Liquids

- Risk of incorrect or accidental overdosing with the device should be discussed and justified in relation to the criticality of the dose for children
- For oral liquid solutions, the max. 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 accuracy of the dosing device.

Oral administration (7)

Suspensions

- Potential for dosing errors of the minimum and maximum should be discussed with regard to sedimentation and sticking of the suspended active substance
- Risk of under-dosing and over-dosing should be discussed (worst case scenario: not shaking the container or not shaking properly)

Drops

- The max. number of drops per single intake should be stated (normally not more than 10 drops)
- Accuracy and precision of the volume should be justified with focus on criticality of the dose

Cutaneous administration

Ointments

- The use of excipients known to sensitize the skin should be carefully justified
- Discussion on the impact of coatings, fever or thermal heating on skin permeability and the risk to overdosing

Transdermal Patches

- If developed to provide for a range of doses/strengths by cutting, cutting lines should be presented (dose uniformity and consistency should be demonstrated)
- Size and shape should be tailored to the size and shape of the child body

Administration in the eye

Eye drops

- In order to avoid preservatives in multi dose preparations, single dose preparations or dedicated multi-dose container that does not require its contents to be preserved are preferable
- Information as to how to hold the container in order to correctly administer the medicine

Parenteral administration

Parenteral dosage forms

- Choice for an intravenous, subcutaneous or intramuscular injection should be justified in the light of child acceptance (pain)
- Justification of needle thickness, needle length, injection volume
- Serial dilutions (in order to achieve the required dose) are not acceptable as they prone to errors
- Size of the syringe and graduation should be described
- Subcutaneous and intramuscular injection volumes should not exceed 1 ml.
- Neonates may only accept very small volumes of medication (volume overload)

Excipients (1)

The following aspects should be considered:

- Pharmaceutical technologic characteristics (potential alternatives)
- Safety profile for children all over the indicated target age groups
- Expected duration of treatment (short term versus long term)
- Criticality of the condition to be treated
- Characteristics of the disease
- Manufacturability
- Allergies and sensitization

Excipients (2)

Risk to benefit evaluation

- Acceptability of the excipient should be based on an overall risk to benefit evaluation
- If excipients with an identified risk cannot be avoided, comprehensive development rationale should be provided taking into account the relative benefits and risks of a number or possible feasible alternatives
- New excipients may be well justified by appropriate pre-clinical studies
- Industry should develop medicines that do not contain excipients known for their potential to cause sensitization/allergies

Excipients (3)

Information sources:

- The Commission, ICH and CHMP guidelines
- CHMP scientific decisions (Q & A paper)
- Excipient composition of currently authorised medicines for children
- Food legislation/European Food Safety Opinions
  - Poses some limitations as it relates to food only
  - Does not apply to neonates
  - Safety of flavours, additives, preservatives requires further evaluation for use in non-oral dosage forms

Excipients (4)

Colouring agents:

- Paediatric medicines should normally not be coloured
- Justification in terms of allergenic potential, minimal toxicological implications

Flavours:

- Palatability plays an important role
- Justification regarding choice of natural versus synthetic flavours

Excipients (5)

Preservatives:

- Lowest concentration feasible should be justified
- Appropriateness of the preservative system for the target age group should be discussed

Sugar/sweeteners

- Effect of sugar content on teeth
- Dosing frequency of the medicine
- Duration of use of the medicine
- Side effects of larger daily exposure (diarrhoea)
- Any effect of the sweetening agent on absorption in the sick child