DEVELOPMENT OF PAEDIATRIC MEDICINES:
POINTS TO CONSIDER IN FORMULATION

BACKGROUND

At the forty-second meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations held on 15-19 October 2007, a draft on Development of Paediatric Medicines: Points to Consider (update of the version dated 14 May 2007) was discussed with a view to contributing to the pharmaceutical part of the document.

This document was prepared by Professor H.G. Kristensen, Denmark and presented a first draft on pharmaceutical development of paediatric medicines. It was based on the above-mentioned paper and the European Medicines Agency (EMA) Reflection Paper: Formulations of Choice for the paediatric population (2006).

An extended revision on pharmaceutical development as a stand-alone text was drafted in February 2008 (working document QAS/08.257). Upon circulation of this document a great number of comments were received. Valuable comments on the pharmaceutical development of paediatric medicines were given, but they also showed that the draft gave too much emphasis on general issues of the development of generic medicines.

A WHO consultation on paediatrics and generics draft guidelines was held in April 2010, resulting in a revision of the guidance on draft pharmaceutical development for multisource (generic) pharmaceutical products (1.4) circulated for comments in June 2010; the first draft was mailed out for comments in June 2008 An outline of the paediatric guidance was discussed at the April 2010 consultation. Another version of the working document was prepared, based on the discussions during that meeting, the feedback and comments received
on the previous version, and the report of the WHO Informal Meeting on Dosage Forms of Medicines for Children, December 2008.

Upon wide recirculation comments were received. This feedback was discussed preliminarily during the Expert Committee meeting in October 2010. A new revision was prepared by Professor Kristensen, taking new trends and development, such as the current efforts undertaken by regulatory authorities, into account. The new proposal was then discussed during an informal consultation held in May 2011. The outcome of that meeting has again been distributed for comments.

**General note**

The “points to consider” document should not detail instructions for development but should rather make reference to relevant literature. Some matters dealt with in the draft on development of multisource products have, therefore, been omitted in this proposal.
1. INTRODUCTION

Safe and effective pharmacotherapy in paediatric patients requires the timely development of medicines and information on their proper use that suit the age, physiological condition and body sizes of the child. Formulations developed specifically for children are often needed. The use of unlicensed and off-label medicines in children is widespread. Their effects on children have not been properly studied, age-appropriate formulations are generally not available, and they are not licensed for use in children.

Pharmacists, parents or caregivers are often faced with the need to manipulate an adult medicine in a way that is not described in the Summary of product characteristics. This can be rather simple, e.g. breaking tablets that do not have a score line with a tablet splitter, or complex, e.g. using tablets as a source for an active pharmaceutical ingredient (API) to prepare a suspension. Pharmacists may also be faced with the need to compound a medicine on the basis of the API.
This process itself can increase the potential for dosage accuracy errors and in general can increase the variability of the product. Such handling may be potentially hazardous for the patient as it may affect the stability, bioavailability and accuracy of dosing of a finished pharmaceutical product (FPP), in particular for controlled-release preparations. The use of such medicines may expose children to overdosing and unintended side-effects or underdosing without the expected efficacy. Moreover, excipients that are safe for adults may not necessarily be so for children.

In December 2007 WHO launched its initiative “Make medicines child size” in order to raise awareness of and accelerate action for the need for improved availability and access to child-specific medicines. The WHO Model Formulary for Children, 2010, provides independent prescriber information on dosage and treatment guidance for medicines based on the WHO Model List of Essential Medicines for Children, first developed in 2007 and reviewed and updated every two years.

Among actions to support the “Make medicines child size” initiative is the present “Points to consider” document on the formulation of paediatric medicines. The scope is to inform regulatory authorities and manufacturers on issues that require special attention in pharmaceutical formulation. Focus is on the conditions and needs in developing countries. The guidance does not provide exhaustive information and does not preclude other aspects relevant to the development of paediatric medicines.

It is not the scope of this document to address extemporaneous preparations and compounding. A separate interim guidance document entitled "Provision by health-care specialists of patient-specific preparations that are not available as authorized products – points to consider" (working document QAS11.399/Rev.1) will supplement and deal with such preparations.

2. PAEDIATRIC DOSAGE FORMS

The paediatric population is a heterogeneous group ranging from newborns to adolescents with large physical and developmental differences regarding pharmacokinetics and pharmacodynamics. Organ maturation, metabolic capacity, skin maturation and other factors may change with age, especially in early infancy (2.1). The age groups identified by ICH
(1.1) have been derived mainly from physiological and pharmacokinetic differences from birth to adult:

- preterm newborn infants;
- term newborn infants (0–27 days);
- infants and toddlers (28 days–23 months);
- children (2–1 years); and
- adolescents (12 to 16–18 years (dependent on region)).

It is a challenge to find one formulation appropriate for all age groups. The aim should be to safely cover as wide an age range as possible with a single formulation. The guiding principle for selecting paediatric dosage forms should be – as for adults – the balance of risk/benefit (1.29) taking into account the specific needs of this vulnerable population.

During the development of pharmaceutical products, the assessment of individual risks related to specific products and starting materials and the recognition of hazards at specific stages of production or distribution, will enable to further enhance the usual quality assurance mechanisms, such as implementation of good manufacturing practices (GMP), by increasing the effectiveness of the activities of all parties involved within the limits of the available resources. Manufacturers who have chosen a more systematic approach to product development would follow the development within the broader context of quality assurance principles, including the use of quality risk management and pharmaceutical quality systems. (Ref.: Quality risk management (1.2) and Pharmaceutical development of multisource (generic) finished pharmaceutical products - points to consider, (1.4).

Current use of medicines for the paediatric population reflects the full range of dosage forms and routes of administration used for adult medicines. Common routes of administration in paediatric patients include oral, parenteral, dermal, pulmonary, nasal, rectal and ocular uses. There is, however, limited information on the acceptability of different paediatric dosage forms in relation to age and therapeutic needs, nor is there sufficient knowledge on the safety of excipients in relation to the development of the child. A European Medicines Agency (EMA) Reflection Paper on paediatric formulations (2.2) provides background information on these issues. Reviews by Ernest et al (2.3) and Krause J and Breitkreutz J (2.4) discuss the needs and challenges in developing paediatric medicines.
Desirable features of quality paediatric medicines common to all dosage forms are outlined below. Further information on specific dosage forms is given in the following chapters.

2.1 Convenient, reliable administration

The administered dose should contain an amount of API adjusted to the age and needs of the child. The implication is that more than one dosage form of the API or more than one strength of a dosage form may be needed to cover different age groups. The intended dose volume or size should be appropriate for the target age group.

Paediatric medicines should preferably be presented as formulations that are ready to administer. The need to manipulate the dose by health professionals, parents or caregivers prior to administration should be kept to a minimum. However, there might be situations, depending on the formulation properties and the dose range to be covered, where this cannot be avoided.

Alternatively, for accurate dosing the dosage form should be designed to subdivide into smaller, uniform doses of appropriate size and in case of liquid forms the dose volume should be accurately measured.

2.2 Acceptability and palatability

Acceptability is the overall acceptance of the dosage form regardless of the mode of administration. Acceptability of a dosage form depends on a variety of factors such as suitability of the dosage form for the particular age group, dosing device for a liquid medicine, palatability of an oral medicine, dose volume or size to be administered, appropriate packaging, clear and accurate labelling information and directions for use. Acceptance of parents and caregivers is also an issue and the cultural setting may influence the understanding of and expectations to the therapy.

Palatability is the overall acceptance of the taste, flavour, smell, dose volume or size and texture of a medicine to be administered to the mouth or to be swallowed. Palatability can be highly important to compliance. Palatability of the API may influence the choice of dosage form and its design, which may include taste-masking ingredients. The dosage form should,
however, not become too attractive to the child (e.g. candy-like as a sugar-coated tablet) in order not to increase risk of accidental poisoning.

It is preferable that the dosage form is palatable in itself without any need for further modifications. The caregiver may, however, attempt to improve the ease of administration and acceptance of the patient by mixing the dose with food or beverages. Mixing with food or beverage should not be encouraged unless it can be done in such a small volume that ingestion of the full dose can be guaranteed and if there are no undesirable physical or chemical interactions between the food and the medicine. If mixing with food or beverage (including breast milk) is foreseen this should be evaluated by appropriate compatibility studies. Information should be provided in the patient information leaflet by the manufacturer, as supported by evidence-based studies.

2.3 Minimum dosing frequency

Parents and caregivers take care of the medication of young children while schoolchildren and adolescents can often manage the medication themselves. In both cases minimal dosing frequency should be attempted. Instructions on the dosing frequency is based on the pharmacokinetic and pharmacodynamic properties of the API, but may be influenced by the design of the dosage form.

Frequent dosing, i.e. more than twice daily, may impact compliance to the dosing scheme for both caregivers and older children, in particular when these are in settings where a trained caregiver is not available, e.g. in school. Moreover, frequent dosing may conflict with the lifestyle of older children.

2.4 End-user needs

In addition to the acceptability and palatability of paediatric medicines it is important that they are convenient to produce and affordable. It is also important to bear in mind supply-chain considerations such as ease of transportation and storage requirements. Storage in a refrigerator by the user is not always possible.
Depending on age and clinical condition of the child, there are restrictions to the applicable dose volume or size. Generally, in developing the product minimum dose volume and size should be attempted.

Lack of access to clean water is an important issue to take into consideration in the development of medicines to be dissolved, diluted or dispersed prior to administration, as it may compromise the quality of an FPP. It may be necessary to educate patients on how to obtain water of suitable quality, e.g. boiling or filtering instructions. Provision of the liquid vehicle as a part of the package may be an option to be considered, or the dose may be dispersed or dissolved in suitable food or beverage prior to administration. Some instructions on such use should be labelled. Regional and cultural differences with regard to preferred taste may need to be considered.

3. DOSAGE FORMS TO BE CONSIDERED IN PARTICULAR

a) Dosage forms that, in general, are likely to prove most suitable for global use, including for developing countries, and which should be prioritized, are flexible solid dosage forms such as tablets that are orodispersible and/or can be used for preparation of oral liquids suitable also for the younger age groups, e.g. dispersible and soluble tablets. The flexible dosage form design may be used for various APIs. They may not be suitable for medicines requiring a precise dose titration.

Provided that the medicine can be dispersed in breast milk from the mother, it could potentially be used in very young children (<6 months). When recommending mixing medicines with breast milk the effect on the taste should be considered as unpleasant taste of medicine may cause aversion in breastfed children. In addition, the compatibility of API and breast milk will need to be considered. The same is valid whenever medicines are mixed with other food.

It is necessary to identify appropriate product strengths and ratios of active ingredients for each medicine as well as ensuring package sizes that allow optimal use under public health programmatic conditions.

b) For oral medicines that require precise dose measurement or titration, suitable dosage forms could be based on a platform technology to produce multiparticulate solids, e.g.
minitablets or spherical granules (pellets), that allow production of dosage forms of varying strength as well as different dosage forms like tablets and capsules, and dosage forms to be dispersed to form a liquid dose or sprinkled onto food. Platform technology has a potential flexibility for constructing appropriate fixed-dose combination products (FDCs). Breakable solid dosage forms specially designed to provide the appropriate dose may also serve (Ref.: (1) Zhao N et al (2010). Tablet splitting: Product quality assessment of metoprolol succinate extended release tablets. Int. J. Pharm., Nov 30, 401(1-2):25-31; and (2) working document QAS/11.399/Rev. 1).

c) For severe disease conditions, e.g. neonatal sepsis, the use of alternative dosage forms should be carefully considered. Some alternatives may be easier to apply by untrained caregivers, e.g. rectal preparation or a spray under the tongue. For some conditions parenteral formulations may be the best existing option; however, their use requires a trained caregiver.

d) As an alternative to parenteral preparations in severely ill children or children unable to swallow, the use of rectal preparations for indications of severe malaria, pain, infection and also nausea and vomiting may be appropriate. There may, however, be cultural barriers to the use of rectal preparations.

4. FORMULATION DESIGN

In the design of paediatric medicines the route of administration, dosage form and dose of the API is decided on the basis of the disease state API properties such as taste, aqueous solubility, pharmacokinetic and pharmacodynamic properties and stability during manufacture, storage and use of the chosen dosage form (2.5). The age, size and condition of the child, e.g. critical illness, concomitant medication, inability to swallow a dose, etc., and the expected duration of the therapy must be taken into account. Selection of the most appropriate dosage form is, therefore, based on case-by-case considerations.

Most medicines are formulated as single compounds. FDCs are chosen only when the combination has a proven advantage over single compounds administered singly such as to achieve compliance in multidrug regimens for HIV and/or TB. The development of FDCs may be more complex than for single compounds; guidance is provided in a WHO guideline (1.3).
4.1 Quality

In the pharmaceutical development of paediatric medicines attention shall be paid to current quality guidelines, especially those provided by the WHO, e.g. guidelines on development of generic products (1.4).

The acceptable level of impurities in APIs and degradation products in finished dosage forms should be qualified and controlled according to regulatory guidelines, e.g. ICH guidelines (1.5, 1.6, 1.7). Safety margins established during toxicological studies on an API and finished dosage form usually apply to worst-case level in adults. Such limits typically apply to both adults and children; although a child would receive a lesser dose, the exposure per kg is likely to be similar. Term and preterm neonates have to be considered specifically and may require safety studies in juvenile animals. Additional guidance may be found on the EMA web site (1.8, 1.9, 1.10).

The final product shall comply with the requirements in relevant pharmacopoeia monographs, preferably The International Pharmacopoeia.\(^1\) With regard to dissolution testing dissolution media should be carefully reconsidered in view of the different gastric pH of the child. Testing in additional pH should be considered in relevant cases. For dissolution testing of special dosage forms such as chewable tablets, suspensions and patches, see the FIP/AAPS guideline for dissolution testing of special dosage forms (2.6).

4.2 Biopharmaceutics classification system

The biopharmaceutics classification system (BCS) is a scientific framework for classification of APIs for oral administration. The BCS is based upon their aqueous solubility and intestinal permeability. An API is considered highly soluble when the highest dose is soluble in 250 ml or less of aqueous media at 37 °C over the pH range of 1.2–6.8. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a medicine to fasting human volunteers with a glass of water. A highly permeable API is absorbed orally to an extent of 85% or more of the administered dose based on a mass-balance determination or in comparison to an intravenous dose (1.14).

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Hence an API can be classified as belonging to one of the four classes: class 1 (high solubility, high permeability), class 2 (low solubility, high permeability), class 3 (high solubility, low permeability) or class 4 (low solubility, low permeability). Classification of APIs included in the WHO Model List of Essential Medicines is provided in the WHO Technical Report Series (1.11).

The BCS may be particularly helpful to assess the importance of aqueous solubility since it relates the solubility of the API to the unit dose. Aqueous solubility should not be of concern in the formulation of immediate-release dosage forms containing class 1 and 3 substances.

For class 2 substances the effect of particle size, polymorphic form, solubility enhancers, etc., should be considered, as the absorption of these substances may be limited by dissolution rate. The same applies to class 4 substances, though factors other than dissolution may also govern the oral absorption. However, overall the BCS classification can be used as a basis when estimating the likelihood of different absorption of paediatric medicines when dosage form and/or used excipients of adult and pediatric medicines differ.

In addition for BCS class 3 and 4 substances, where also the absorption process and/or intestinal first pass restrict bioavailability, excipients affecting transit time (efflux), transporter function and metabolic enzymes (typically CYP3A4) should be taken into consideration.

### 4.3 Excipients

The use of excipients in paediatric medicines is driven by functional requirements and should be justified through a risk-based assessment, taking into account amongst others the paediatric age group, frequency of dosing and duration of treatment.

The added challenge for paediatric medicines compared to adult medicines is that excipients in children may lead to adverse reactions that are not experienced in adults or not seen to the same extent. Reviews on adverse reactions attributed to excipients show that the currently available data on excipient safety are of limited quantity and variable quality.
Major problems with excipients in paediatric medicines, especially in infants and neonates, have been reported (2.7), e.g. for benzyl alcohol, azo-dyes, propylene glycol, ethanol and propyl paraben. A study on the exposure of benzyl alcohol and propylene glycol to neonates receiving parenteral medication demonstrated a potential risk of toxic doses, especially for neonates receiving continuous infusion (2.8). The toxicity of excipients in newborns and infants can be explained by factors related to the physiological and metabolic development (2.1). Information on the safety of some excipients may be found, for example, in reviews published by the American Academy of Pediatrics (2.9). Other alternative sources of information should also be considered, e.g. the WHO Technical Report Series on Evaluation of Certain Food Additives (2.10).

In the development of paediatric medicines the number of excipients and their level in a formulation should be the minimum required to ensure an appropriate product with respect to performance, stability, palatability, microbial control, dose uniformity and other considerations to support product quality. Risks for adverse reactions are mostly associated with excipients used for liquid dosage forms.

In the choice of excipients consideration should be given to:

- the safety profile of the excipient for children of the target age groups;
- the route of administration;
- single and daily dose of the excipient;
- duration of the treatment;
- acceptability for the intended paediatric population;
- potential alternatives;
- regulatory status in the intended market.

Potential alternatives to excipients posing a significant risk to a child should always be considered. Another dosage form or even route of administration might be necessary to avoid significant risk. Although well-known excipients with well-defined safety profiles are preferred, new excipients cannot be excluded. Novel excipients should only be used when safety, quality and appropriateness of use in children have been established. In addition, alternative excipients may need to be considered because of different cultural or religious reasons, e.g. the use of gelatin may not be acceptable for all patients.
4.4 Colouring agents

The use of colouring agents in paediatric medicines is generally discouraged, in particular for infants and young children. Their use may, however, be justified in certain cases, e.g. to avoid accidental dosing errors in connection with medicines produced in several strengths. In this case, a solid dosage form of the types mentioned in section 3 may be preferred because size, shape and embossing can facilitate identification of different strengths of the preparation.

Concerns on the safety of some colouring agents in paediatric medicines have been associated with hypersensitivity (2.11). The number of colouring agents that are acceptable for use in medicines is limited. Azo-dyes should be avoided in paediatric medicines and consideration should be given to the risk of allergic reactions associated with natural colourants (2.12).

4.5 Antimicrobial preservatives

FPPs may need antimicrobial preservation to avoid microbiological proliferation arising under storage, in particular under in-use conditions. Preservation is needed in particular for aqueous multidose preparations and semi-solid preparations and may also be needed for other aqueous preparations. Usually solid dosage forms do not need preservation.

Preservatives may have a potential to cause adverse reactions, in particular in infants and neonates, and should be avoided when possible. Furthermore, complex preservative systems should be avoided.

Ophthalmic preparations without preservatives are strongly recommended for use in children, especially neonates. Therefore, preparations without preservatives should be developed wherever possible in order to cater for the diversity of patients’ needs. When preservatives are required the concentration should be at the minimum level consistent with satisfactory antimicrobial function in each individual preparation and a thorough justification for the choice of the preservative should be established. Ophthalmic preparations without any mercury-containing preservatives, e.g. thiomersal, should also be considered. Further details on this topic are provided in a public statement (1.12) published on the EMA web site.

4.6 Sweetening agents
Palatability of oral paediatric medicines often requires the use of sweetening agents like cariogenic and non-cariogenic sweeteners. In addition to the considerations listed in section 4.3 attention should be paid to:

- safety of the sweetening agent in relation to specific conditions of the child, e.g. diabetes, fructose intolerance, use of aspartame in patients with phenylketonuria;
- the laxative effect of poorly absorbed or non-digestible sweeteners in high concentrations;
- the severity of the condition to be treated, i.e. are potential adverse reactions of the sweetening agent secondary to patient compliance?

4.7 Taste masking

Taste masking of medicines for oral use or use in the mouth is often needed to improve palatability of the medicine. Children have a well-developed sensory system for detecting tastes, smells and chemical irritants and are able to recognize sweetness and saltiness from an early stage and also able to recognize sweet taste in oral liquids and the degree of sweetness (2.13). Children seem to prefer higher levels of sweetness than adults. The unpleasant taste of an API, e.g. bitterness, metallic taste, is, therefore, often masked in an oral liquid by the use of sweetening agents and flavours. Additional use of colouring agents that match the flavour is discouraged (see section 4.4) unless it is necessary to cover API-related unpleasant colour. Some successful approaches to taste masking are discussed by Ernest et al (2.3).

Children’s preference for flavours is determined by individual experiences and culture. The target for taste masking need not necessarily be good-tasting medicines, just acceptable taste, to account for cultural differences in taste and a taste acceptable to as many countries as possible.

An example of a "qualitative evaluation of the taste by a taste panel" for zinc formulations can be found in the UNICEF/WHO publication on production of zinc formulations (Production of Zinc Tablets and Zinc Oral Solutions, Guidelines for Programme Managers and Pharmaceutical Manufacturers, Annex 7, World Health Organization, 2007; and (2) Cram A et al (2009) Int. J. Pharmaceutics (365), 1-3).

Consideration should be given to the items listed in sections 4.3 and 4.6.
Taste masking of orodispersible tablets and chewable tablets is in principle similar to taste masking of oral liquids. Non-cariogenic sweeteners and flavours are preferred.

### 4.8 Solubility enhancers

The aqueous solubility of the API may limit the achievable concentration in formulated solutions and, hence, the desirable dose volume. In many cases an acceptable solution requires the use of solubility enhancing methods, e.g. use of non-ionic surfactants and use of cosolvents such as glycerol, liquid macrogols and ethanol. In the use of solubility enhancers safety considerations should be given to both the agent as such and the formulation, for example, risk of irritation and damage of intestinal tissues in neonates caused by hyperosmolality or other local toxicity. Risks associated with the use of solubility enhancers are higher when included in parenteral preparations than oral preparations.

Ethanol, especially large amounts, should not be administered to children (0-17 years) through FPPs without a clear demonstration of benefit. Although it is recognized that ethanol may not always be eliminated from FPPs and replacements may raise other issues, the smallest amount should be used. When ethanol is used adequate development data demonstrating that the lower concentration of ethanol is used should be established.

Children are more vulnerable to the effects of ethanol, especially in the younger age groups of less than 6 years. Adverse central nervous system effects are already reported with blood ethanol concentrations of 10 mg/100 ml in children. Higher peak ethanol blood concentrations are also observed in children compared to adults for similar intake. Chronic exposure to ethanol (>1 week), even small doses, through FPPs is in principle contraindicated below 6 years and limited to 2 weeks above 6 years, if a positive risk/benefit balance is not demonstrated. Toxicity on brain maturation in young children is highly probable and also supported by non-clinical data. Additionally, chronic exposure has been shown to be linked to dependence in adults and adolescents.

### 5. ORAL ADMINISTRATION

The oral route is the most preferred and most appropriate route of administration to paediatric patients. It is generally acceptable in all age groups if administered in a suitable dosage form, e.g. in liquid form for the youngest age groups which have difficulties in swallowing solid
dosage forms. Strictly, the choice of oral administration depends on the gut function and, thus, on both age and clinical condition.

Consideration should be given to effects of increased gastric pH and intestinal mobility at birth and early infancy (1). In addition, gastric emptying of sick newborns is most erratic and can be delayed. Further information can be found in an EMA guideline concerning term and preterm neonates (1.13).

Mixing oral dosage forms with food or beverage is not preferred but may be performed to enhance compliance (see section 2.2). Potential effects of foods on bioavailability should be considered. When recommending mixing medicines with food the effect on the taste should be considered as an unpleasant taste of medicine may cause aversion in children.

### 5.1 Oral liquid preparations

Oral liquid preparations include aqueous solutions, suspensions, emulsions and syrups. They are most appropriate for the youngest age groups which are unable to swallow solid dosage forms. The advantage of oral liquid preparations is that variable dose volumes can be measured and administered. The need for the use of stabilizing agents, e.g. antimicrobial preservatives, is a major drawback as is the potential chemical instability, which may require controlled storage conditions during distribution and use. Oral liquid preparations are less transportable than solid-dose preparations because of the relative high bulk volume.

The dose volume is important for the acceptability of the preparation. High-dose volumes give rise to risk for incomplete ingestion and, thus, under-dosage. Efforts should, therefore, be made during pharmaceutical development to minimize the dose volume while recognizing the need to assure accurate measurements of the dose over the anticipated range. Typical target dose volumes are 5 ml or less for children under 5 years and 10 ml or less for children of 5 years and older (2.14). There is some uncertainty on these limits because the more palatable the formulation, the higher dose volume will be accepted by the child. Target volumes and electrolyte contents are critical for neonates, especially in cases of immature renal function.
Oral liquid preparations may be supplied in multidose containers or single-dose containers. Usually, both forms require antimicrobial preservation. Special attention has to be paid to the in-use stability of multidose preparations, both microbial and physical-chemical stability.

Multidose preparations should be packaged together with an appropriate dosing device. The correct graduation of the device and the accuracy of the volumes measured must be checked by the manufacturer. Generally oral syringes are preferable because of the flexibility in dose measurement and superior accuracy compared to graduated pipettes, plastic spoons, etc. The accuracy in measuring and delivering a volume of liquid is influenced by the liquid's physical characteristics, especially its viscosity.

The risks associated with incorrect dosing should be considered. If critical, a single-dose preparation, e.g. a pre-filled oral syringe, should be considered.

*Drops*

Some liquids are administered as drops in small volumes using a dropper or a graduated pipette to measure a volume to be dissolved or dispersed in water or another diluent before swallowing the dose. The use of this dosage form should be evaluated using a risk-based approach to ensure it is suitable given the drug’s potency and side-effect profile and the potential for dosing errors. The in-use performance of the dose-measuring device is critical for this dosage form.

*Oral suspensions*

Formulation of an oral suspension may be dictated by the aqueous solubility of the API and the balance between the dose of API and the dose volume. In certain cases, the unpleasant taste of an API can be reduced by choosing the suspended form.

Oral suspensions must be shaken before use to ensure a homogeneous liquid when the dose volume is measured. There might be in some instances a significant risk for dosing errors due to sedimentation or caking of the suspension during storage; therefore, resuspendability should be a stability parameter. The control strategy for oral suspensions includes dissolution testing (2.6) unless otherwise justified.

*Powders and granules for reconstitution*
Solid preparations for reconstitution as solutions or suspensions should be considered especially when the liquid preparation possesses a short shelf-life due to instability (chemical, physical, microbiological). Powders and granules for reconstitution are single-dose sachets or multidose preparations, usually provided in containers that can hold the reconstituted multidose preparation. The liquid vehicle can be provided together with the dry preparation, especially when the product is intended for markets where access to clean water may be difficult. Alternatively, manufacturers can recommend on the product labels and summary of product characteristics (SmPCs) how to reconstitute the product, e.g. with boiled and cooled water.

To secure the proper use the solids must be easily wetted and dispersed or dissolved within a short time when the vehicle is added.

Major drawbacks of this type of formulation are the bulk volume of the preparation, i.e. less transportable, and the in-use microbial stability of multidose preparations, which may require use of antimicrobial agents. For these reasons, single-dose preparations of the flexible types mentioned in section 3a are preferable.

5.2 Administration through feeding tubes

In neonates and seriously ill infants enteral administration of liquids via feeding tubes is used. Hence the preparation will not be subject to the normal effects of saliva and/or gastric juice, which may affect bioavailability.

Dosing accuracy should be considered, taking into account the ease of transfer along the feeding tube (viscosity, particle size and amount of suspended components, etc.), potential absorption of API into the tube material and rinsing by flushing of the tube. The rinsing volume should be relevant to the target age group and acceptable fluid intake.

These considerations should be highlighted in the SmPCs.

5.3 Oral solid dosage forms

Oral solid dosage forms include a variety of final forms from powders to coated tablets intended to be swallowed directly or after application to the mouth (chewable tablets, orally
dissolving tablets, orodispersible tablets). Some are intended for swallowing after dissolution, dispersion in water or other suitable liquids. The advantages over oral liquid preparations are improved stability, good dosage uniformity and options for different doses. The ease of administration depends on the child and the particular dosage form. They are convenient for packaging and transport.

While powders and multiparticulate preparations mixed with food or beverages may be acceptable from the moment when the infant is able to accept solid food, i.e. about 6 months, there are uncertainties with regard to the age where intact tablets and capsules are acceptable. It has been thought generally that even small tablets and capsules to be taken as whole are not acceptable below the age of 6 years. However, no good scientific evidence exists. Recent preliminary evidence indicates that mini-tablets (below 4 mm) may be acceptable even for the majority of small children (2–4 years old) (2.15).

**Powders and multiparticulate preparations**

Powders and multiparticulates are provided in sachets or hard capsules that allow the contents to be taken directly or after manipulation, e.g. preparation of oral liquids or to be sprinkled on to food or liquids.

Multiparticulate preparations are granules, rounded granules of uniform size (often called pellets) and mini-tablets. Pellets are often prepared by extrusion/spheronization technology into uniform particles within the size range of 0.5–2 mm. Mini-tablets are prepared by compression into units with a diameter of not more than 4 mm. Especially when only a portion of the provided dose is administered the particle size distribution of the API may be critical to dosing accuracy. Dose uniformity control should be performed on a level corresponding to the dose to be taken by the target age group.

Multiparticulate preparations possess the same advantages as conventional tablets and capsules with regard to the use of excipients, opportunities for taste masking, e.g. by coating, stability and opportunities for modifying the release profile. Furthermore, they possess great flexibility. An age-related dose may be obtained by taking a number of pellets or mini-tablets. A counting device may be necessary when a larger number of particles is required. In addition, pellets and mini-tablets are suited for the platform technology mentioned in section 3b.

**Immediate-release tablets**
Conventional tablets are either uncoated, film-coated or sugar-coated and are intended for immediate disintegration, release and absorption when swallowed. The coating may cover an unpleasant taste and smell and will in general improve palatability. Film-coating is preferable because sugar-coated tablets are candy-like and hence may be too attractive for the child. It is critical to differentiate the appearance of tablet packs from confectionary packs.

Break-marks intended to permit accurate subdivision of the tablet to provide doses of less than one tablet should be proven to result into parts that comply with the requirements for uniformity of mass or uniformity of content, as appropriate. The decision whether or not to provide scored tablets will depend on a risk analysis, taking into account the safety and dose of the API. A suitable test is provided in the monograph on tablets in *The International Pharmacopoeia*. It is preferable that the single part of the broken tablet contains the amount of API suited to the youngest intended age group. Specially designed tablets and tablet punches may be needed for the purpose.

Caregivers often crush tablets to increase user-friendliness and compliance. It may, however, affect the bioavailability of some medicines. The effect of crushing of tablets should be investigated by the manufacturer and this information should be provided in the patient information leaflet.

Crushing of tablets should not be done unless instructions allowing crushing are labelled by the manufacturer. Generally a multiparticulate formulation provided in sachets, hard capsules or blister is preferred.

**Chewable tablets**

Chewable tablets are intended to be chewed and swallowed. They should possess good organoleptic properties including a good mouth feel, which is influenced by the solubility, particle size and shape of the API, and do not leave a bitter or unpleasant after-taste. They are usually formulated with a high content of a water-soluble sweetener such as mannitol that provides a sweet, cooling taste, and microcrystalline cellulose, which assists in obtaining a good mouth feel and reduces grittiness. Other sweetening agents such as sorbitol and xylitol suitable for direct compression are also used.

A potential problem with chewable tablets is that they may be swallowed by a patient without proper chewing or chewing at all. It is, therefore, strongly recommended that chewable tablets
are formulated so they may be swallowed whole and, thus, labelled as “tablets that may be chewed or swallowed whole”, or “tablets that may be chewed, swallowed or crushed and mixed with food or liquid”.

It is a consequence of the above that tablets that may be chewed or swallowed whole meet the quality requirements for conventional tablets including dissolution testing. Where applicable, dissolution test conditions should be the same as used for conventional tablets of the same API, but because of the non-disintegrating nature it may be necessary to alter the test conditions (2.6).

Effervescent dosage forms
Effervescent dosage forms are tablets, granules or powders that are dissolved in water prior to administration. The use of these dosage forms usually requires a relatively large volume of water, the intake of which may be problematic for children. It is helpful when an indication of the minimum volume of water is labelled. Furthermore, the label should instruct not to drink the solution before effervescence has subsided in order to minimize ingestion of hydrogen carbonate. Effervescent tablets require continuous attention to moisture and humidity during manufacture, packaging and storage.

Drawbacks of effervescent dosage forms are the need for clean water for dissolution and the ingestion of potassium or sodium, which may make them unsuitable for patients with renal insufficiency.

Dispersible and soluble tablets
Dispersible and soluble tablets are intended for use in the same way as effervescent tablets. The advantage is that problems with hydrogen carbonate, potassium and sodium are avoided. For the convenience of users, the formulations shall disintegrate or dissolve within a short time when added to water. It is helpful when an indication of the minimum volume of water is labelled.

Dispersible and soluble tablets are flexible dosage forms, the formulation of which may be suited for several water-soluble APIs (see section 3a).

Sustained-release formulations
Sustained-release formulations are designed to slow the rate of release of the API in the gastrointestinal fluids. They may be provided in a variety of formulation designs, e.g. multiparticulate solids provided with a barrier coating, in sachets, hard capsules or in quickly disintegrating tablets, coated tablets and matrix tablets. Among the advantages of the sustained-release design is the reduced dosing frequency compared to conventional formulations of the same API, which may improve compliance (see section 2.3). Not all APIs can be formulated as sustained-release products. This will also depend on other factors regarding aqueous solubility, intestinal permeability and plasma elimination half-life, which may differ from those of adults.

In the development of sustained-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 emptying rate, intestinal mobility and their variability.

A majority of sustained-release formulations, especially coated tablets and matrix tablets, must not be broken or chewed and some do not withstand being mixed with food or beverage. It is, therefore, a necessity that clear instructions on the proper use of the formulation are included on the label.

**Capsules**

Capsule formulations are provided as soft capsules, usually with a liquid or semi-solid content, and hard capsules containing powder or a multiparticulate formulation.

Capsules may be taken as a whole. The limitations mentioned for tablets apply with regard to the ability of the child to swallow (see introduction of section 5.3). Hard capsules may be opened and their contents taken as such or taken after mixing with food or sprinkling on to food, but this is not always appropriate.

Instructions on the proper use of a capsule formulation should be labelled, e.g. whether the capsule has to be taken as such and/or the capsule contents can be mixed with food to facilitate intake and palatability.

**Orodispersible dosage forms**
Orodispersible dosage forms are orodispersible tablets, oral lyophilisates and thin films, to be placed on the tongue where they disperse rapidly into small-sized particles or “melt” by dissolution in the saliva, whereafter the dose is swallowed.

Orodispersible tablets having fast-disintegrating properties are prepared by compression of a formulation containing, for example, mannitol, a super-disintegrant, and a flavouring agent. The amount of API that can be incorporated depends on the physical properties of the API. The product may be moisture-sensitive. Orodispersible tablets are flexible dosage forms, (see section 3a), suited especially for highly water-soluble APIs.

Oral lyophilisates are prepared by freeze-drying of aqueous liquids into porous units shaped like tablets. Typical excipients are gelatin or alginate as structure-forming agents, and mannitol, which facilitates formation of the porous structure and contributes to a palatable dose. Instead of mannitol, sorbitol may be used as a crystallization inhibitor. The amount of water-soluble API to be incorporated is limited. Oral lyophilisates are sensitive to moisture and require a vapour-tight package.

Thin, flat films (wafers) to be placed in the oral cavity are prepared by casting water-soluble polymers containing the API in dissolved or dispersed form. The amount of dissolved API that can be incorporated is limited. The release profile depends on the polymer, film thickness and API solubility. The so-called flash-release wafers may have dissolution times of less than 30 seconds.

Orodispersible and orosoluble dosage forms are attractive for several reasons. They may be acceptable to the same age groups as liquid preparations, and it is possible for children, who cannot swallow a whole tablet, to take an orodispersible dosage form. In some situations, especially with younger children, the orodispersible dosage form may need to be dissolved in a small volume of liquid prior to administration.

Orodispersible dosage forms are intended for systemic effect after being swallowed but absorption may also take place in the mouth and pharynx. Taste masking may be necessary by the use of water-soluble sweeteners and flavours.

6. RECTAL ADMINISTRATION
Rectal administration is an important route of administration that can be used for both local (e.g. laxative and anti-inflammatory) and systemic effects (e.g. antipyretic and anticonvulsive) in all age groups. The route of administration is especially valuable when oral administration is not possible because of the condition of the child and palatability issues. In certain cases it is possible to obtain immediate systemic effect by rectal administration of solutions. There is, however, limited absorption and bioavailability for many APIs. Erratic absorption due to faecal contents in the rectum may variably delay absorption.

Dosage forms for rectal administration are primarily suppositories, rectal capsules and rectal liquids (enemas). Other dosage forms are available, e.g. rectal foams provided in pressurized containers.

When suppositories and rectal capsules are administered to paediatric patients there is a risk of premature expulsion, especially when the dosage form constituents have an irritating effect. Rectal dosage forms should be used with extreme caution in the premature population, as they can tear very delicate tissues and, thus, introduce infection.

Concordance and compliance of rectal preparations may be lower than for oral dosage forms. There are barriers to rectal administration for both caregiver and patients in some regions and cultures. Generally the acceptability among children of any age is poor.

6.1 Suppositories

Suppositories for use in paediatric patients must be tailored to the age or size of the child. Cutting of suppositories into halves should be avoided unless they are designed to be cut. The majority of suppositories contain APIs as solid particles, which may be unevenly distributed in the suppository base due to the manufacturing technique by moulding a molten formulation. However, it is also possible to prepare suppositories which can be cut in smaller portions, ensuring delivery of appropriate dose. Information on acceptability of cutting suppositories should be provided. When designed to be cut information on the technique should be provided in the patient leaflet.

Two types of suppository bases are available: (i) insoluble in water, e.g. hard fat, which melts below body temperature; (ii) soluble or miscible with water, e.g. macrogols, which are
dissolved in or mixed with the rectal liquid. Both types may be irritating. With suppository melt formulations special consideration has to be given to storage temperature.

6.2 Rectal liquids (enemas)

Rectal liquids are solutions, suspensions or emulsions based on water or vegetable oil. Any volume to be administered should be adapted to the size of the child. For systemic therapy the volume to be administered should be as small as possible to achieve accurate delivery, good absorption and absence of irritation. Volumes of 1–5 ml may be acceptable.

The rectal tube should be of a length appropriate to the size of the child and should not cause injury. Use of pre-filled syringes equipped with a rectal tube facilitates individual dosing and may reduce the need for several strengths of the formulation.

Formulation of aqueous rectal liquids has the same feature as formulation of other aqueous liquids, i.e. use of stabilizing agents including surfactants and antimicrobial agents. Non-ionic surfactants are preferred because ionic surfactants are frequently irritating to the rectal mucosa. The need for stabilizing agents, in particular antimicrobial agents, may be reduced by the formulation of rectal tablets to be dispersed or dissolved in water immediately before administration.

7. PARENTERAL ADMINISTRATION

Parenteral administration by the intravenous route is the preferred route of administration for seriously ill children and for clinically unstable term and preterm neonates (in developed world settings). Some parenterals are administered by the subcutaneous (sc) and intramuscular (im) routes. The limited muscle mass of newborns and in particular preterms constrains the use of im injections. Other routes of administration, e.g. intraosseous, are used in emergency cases.

Most children have a fear of injection needles. Possible alternatives, especially suited for frequent or long duration of treatment, such as needle-free injection devices (jet injectors), that drive small droplets through the skin by high pressure, could be considered, e.g. for sc administration. However, there is only limited experience currently available on their use in paediatric populations, especially with smaller children.
Repeated injections should preferably be avoided in children unless they can be given iv via catheter/injection ports that can remain in place for the length of the treatment. Reducing the number of injections by formulation of sustained-release preparations requires consideration of increased blood perfusion in children, usually increasing absorption from tissue depots. The clinical need to limit fluid uptake, especially in very young children, must also be considered.

The availability of age- and weight-related preparations (injection volume and strength) is preferred in order to take into account the acceptable injection volume, and to avoid dosing errors due to improper use of multidose preparations and calculation errors in dilution to obtain measurable volumes. It is helpful to include on the label the size of syringe that permits accurate administration.

The size of the presentation should not allow significant overdosage if the dose or volume is miscalculated. In general the volume in the vial should be no greater than 10 times the smallest dose to be measured.

**Formulation**

Aqueous preparations (solutions, suspensions) must be adapted to the physiological conditions on the application site. The tolerances for deviations in pH and osmolality are dependent on the route of administration. In particular, sc administration is highly sensitive because dilution of the injected volume and its escape from the injection site proceed slowly. Hyperosmolar injections and injections with extreme pH may cause pain and irritate peripheral veins.

Formulations for neonatal patients are usually aqueous solutions intended for iv administration. Target volumes and electrolyte contents are important for all paediatric patients, however critical for neonates (1.14).

It is highly important to consider the safety profile of each excipient and its suitability for the intended use (see section 4.39).
Consideration should be given to the potential adsorption of the API on to surfaces of plastic containers and catheters, and leaching of plasticizers from containers and catheters to the parenteral preparation.

Some APIs are presented as powders or lyophilisates to be reconstituted prior to administration. It is important that clear instructions on the reconstitution and information on storage conditions and time are labelled.

**Additional points to consider for parenteral preparations**

- There should be a minimal requirement for complex calculations for prescribing, dispensing and administration (e.g. dose in microgram/kg/hour prescribed to be converted to volume per hour administered; conversion between mmol prescribed and mg on the label; conversion between mg prescribed and % concentration on the label; decimal fractions).
- There should be a minimal need for additional steps in the preparation of the product for administration, for example, by developing ready-to-use preparations.
- Measurement of volumes less than 0.1 ml should not be required. Dose volumes in hundredths of a ml should be avoided. Tables should be included in the product information clearly stating the dose, volume to be measured and how this can be achieved safely and accurately.
- Miscalculation can lead to overdose and the amount of the API in the presentation should not allow a critical overdose to the smallest patient for whom the presentation is intended.
- Using several vials per dose or large vials that may contain several doses should be avoided if possible.
- Other methods of preventing overdose of critical medicines can be explored and presented for consideration, e.g. tables of weight, dose (mass) and volume (ml) of preparation required.
- Safety and restrictions should be provided on administration via central or peripheral cannula including advice on maximum and minimum dilutions for safe administration;
- There should be contribution to the child’s fluid and electrolyte balance due to the medicine administration volume and/or electrolyte content.
Compatibility with other medicines that are part of a standard care should be investigated.

Information on pH of the FPP needs to be provided in the product information.

8. DERMAL AND TRANSDERMAL ADMINISTRATION

Preparations for dermal (or cutaneous) administration include liquid preparations (lotions, shampoos), semi-solid preparations (ointments, creams) and solid preparations (powders). They are used to obtain local effects.

Unintended systemic absorption through the dermis is a potential risk for many APIs. The stratum corneum is deficient in pre-term neonates. Children have a lower volume of distribution per unit area of skin.

Dependent on the dosage form, various excipients are needed. The safety profile of each must be considered (see section 4.3) including the risk to sensitize the skin. Preparations containing ethanol should be avoided in very young children because ethanol may dehydrate the skin and cause pain.

Liquid suspensions, semi-solid preparations and patches should be subject to dissolution testing (2.6).

8.1 Transdermal patches

Transdermal patches are used for systemic delivery of APIs which are capable of diffusion through the stratum corneum and therapeutically active in the low plasma concentrations that can be achieved. Today the manufacture of transdermal patches of “drug-in-adhesive” type is well developed and less problematic than the originally developed “drug-in-reservoir” type; the API is dispersed in a suitable polymeric adhesive to be fixed in a thin layer on a backing and covered by a removable liner.

The size and shape of a transdermal patch should be adapted to the child's body. It should stick firmly to the skin and not be too difficult to remove. Application sites which cannot easily be reached by the child should be considered in order to avoid removal of the patch by the child. The risk for deliberate removal and its consequences for therapy must be considered.
The increased systemic absorption through the skin for the reasons mentioned above may increase the systemic delivery from transdermal patches, in particular in newborns and young infants.

When designed to be cut, information on the technique should be provided in the patient leaflet and facilitated by the presence of cutting lines to ensure equal division. Reservoir systems should never be cut.

Adhesives should have a low allergenic potential to avoid irritation and infection. Local tolerance and acceptability should be tested.

9. INHALATIONS

Pulmonary administration of medicines by inhalation is used traditionally to obtain a local effect. This route of administration also has a potential for systemic delivery. Preparations for inhalation include liquids for nebulization, pressurized metered dose inhalers (MDIs) and dry powder inhalers (DPIs).

The implications of physiology of children and their ability to use the devices correctly should be considered in the development of paediatric inhalations (2.4). Depending on their age, children may have more or less difficulties with some of the devices. Problems with the coordination of the inhalation for MDIs and the ability to inhale strongly enough for DPIs determine the effectiveness of getting the drug into the lung.

The total lung deposition is important for the clinical efficacy of preparations for inhalation. Generally it is affected by the formulation and delivery device controlling size distribution of the aerosol and patient-related factors such as the current disease state. The airway diameter is smaller in children than in adults; hence deposition by impact in the upper and central airways may be significantly higher in children (2.17). The particle size of the aerosol produced by the delivery device needs to be explored during development.

Nebulized liquids are potentially suitable in young children who cannot use MDIs and DPIs. Their use requires, however, nebulizing devices and access to electricity.
MDIs may be suitable for children from birth when combined with a spacer. A spacer eliminates the need for coordinating the MDI actuation and the start of inhalation. For children younger than 2–3 years a facemask is also required. This can be replaced by a mouthpiece when the child is able to manage the system.

DPIs may be used in children from the age of 4–5 years as minimum inspiratory flow is required. DPIs and MDIs are preferred in older children because of their portability and convenience.

10. PACKAGING AND LABELLING

Container-closure systems for paediatric medicines are designed and constructed from materials meeting relevant regulatory requirements, and taking into account the stability of the medicine during transport, storage and use. In addition they are designed with a view to:

- accurate dosing and convenient administration of the medicine;
- be robust and convenient for the supply chain, i.e. transportable;
- be tailored to the target age group;
- contribute to in-use stability;
- give appropriate information on the use of the medicine.

In cases where the paediatric medicine is significantly different from a similar adult medicine, it would be important for the product packaging to be noticeably different between the two products. It should be considered whether the medicine is to be packed in a child-resistant container, i.e. a packaging difficult for young children to open but not unduly difficult for adults to open properly.

Self-administration of medicine in schoolchildren and adolescents is facilitated when:

- the medicine is easy to use;
- separation of the day dose pack is facilitated, which should be easily carried by the patient in his/her bag;
- clear instructions for use are contained therein.

Adequate information about the medicine and how to use it are important. Information about the dosage should be clearly spelt out, e.g. as milligrams per weight. Specific instructions
about how to measure and administer a precise dose should be provided. Drawings or pictograms showing time, method and route of administration are strongly recommended.

11. GLOSSARY

Child-resistant container
A packaging difficult for young children to open but not unduly difficult for adults to open properly.

Flexible dosage form
A solid dosage form that can be administered to patients in more than one manner, e.g. be dispersed or taken orally as a whole.

Labelling information
Information to the user provided on the package label or in the patient information leaflet.

Mini-tablet
A tablet of no more than 4 mm diameter.

Off-label use
Use of a medicine outside of the scope of regulatory authorization.

Platform technology
Technique, including formulation and related processes, that can be used to obtain different dosage forms, different strengths and/or accommodate different APIs.

12. REFERENCES

[Note from the Secretariat:
The references will be adjusted to the usual WHO style in the final version.]

1. Guidelines

1.1 Clinical Investigation of Medicinal Products in the Paediatric Population, ICH Topic E11.
1.2 WHO draft guideline on quality risk management (working document QAS/10.376).


1.4 Pharmaceutical development for multisource (generic) pharmaceutical products (working document QAS/08.251/Rev.1).

1.5 Impurities in New Drug Substances, ICH Topic Q3A(R2).

1.6 Impurities in New Drug Products, ICH Topic Q3B.

1.7 Impurities: Guideline for Residual Solvents, ICH Topic Q3C.

1.8 Guideline on the Limits of Genotoxic Impurities (CPMP/SWP/5199/02).

1.9 Q&A on the CHMP Guideline on the Limits of Genotoxic Impurities (EMEA/CHMP/SWP/431994/2007).

1.10 Specification Limits of Residues of Metal Catalysts (CPMP/SWP/QWP/4446/00).


1.12 Public Statement on antimicrobial preservatives in ophthalmic preparations for human use (EMEA/622721/2009).


2. Literature


3. Web sites – referred to in this document

WHO World Health Organization: http://www.who.int

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