

DEVELOPMENT OF PAEDIATRIC MEDICINES: POINTS TO CONSIDER IN PHARMACEUTICAL DEVELOPMENT

REVISED DRAFT (Rev.1) FOR COMMENT

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 Henning 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 showed also that the draft gave too much emphasis on general issues of the development of generic medicines. Work on a guideline on pharmaceutical development of multisource (generic) products was in progress with a first draft from June 2008.

A WHO consultation on the paediatrics and generics draft guidelines was held in April 2010 resulting in a revision of the generic guideline (Working document QAS/08.251/Rev.1) circulated for comments in June 2010. An outline of the paediatric guideline was discussed at the April 2010 consultation. The present draft is prepared according to the outcome of this discussion and with a view to the report of the WHO Informal Meeting on Dosage Forms of Medicines for Children, December 2008.

A "points to consider" document should not detail instructions for the development but should rather make references to relevant literature. Some of the matters dealt with in the draft on development of multisource products have, therefore, been omitted in this proposal.

Please address comments on this revised proposal, by 30 November 2010, to Dr S. Kopp, Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int with a copy to gaspardm@who.int.

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**DEVELOPMENT OF PAEDIATRIC MEDICINES: POINTS TO CONSIDER IN
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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. When child-specific medicines are not available, parents and caregivers have to use fractions of adult dosage forms or prepare doses for children by using portions of crushed tablets or capsule contents that are dispersed in

water or another suitable liquid. Pharmacists are often faced with the need to extemporaneously manipulate adult medicines or active pharmaceutical ingredients (API) to provide medicines for paediatric use. These practices are potentially hazardous for the patient in terms of product stability, bioavailability and accurate dosing and may expose children to over-dosing and unintended side-effects or under-dosing without the expected efficacy. Moreover, excipients that are safe for adults are not necessarily so for children.

WHO launched in December 2007 its initiative “Make medicines child size” in order to raise awareness and accelerate action to 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” guidance on pharmaceutical development of paediatric medicines. The scope is to inform regulatory authorities and manufacturers on issues that require special attention in the pharmaceutical development of paediatric medicines. 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.

2. PAEDIATRIC DOSAGE FORMS

The paediatric population is a heterogeneous group ranging from newborns to adolescents with large physical and developmental differences regarding absorption, pharmacokinetics and pharmacodynamics. Organ maturation, metabolic capacity, skin maturation and other factors may change with age, especially in early infancy [1]. The age categories identified by ICH¹ have been derived mainly from physiological and pharmacokinetic differences from birth to adult. It is hardly possible to find one formulation appropriate for all age groups. 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. Neither is there sufficient knowledge on the safety of excipients in relation to the development of the child. An EMA Reflection paper on paediatric formulations [ii] provides background information on these issues. Reviews by Ernest et al. [iii] and Krause and Breitzkreutz [iv] discuss the needs and challenges in developing paediatric medicines.

Desirable features of quality paediatric medicines common to all dosage forms are outlined in the following. Further information on specific dosage forms is given in the following chapters.

2.1 Convenient, reliable administration

¹ ICH Topic E11, Clinical Investigation of Medicinal Products in the Paediatric Population.

Paediatric medicines should preferably be ready-to-use formulations. Manipulation of the dose (e.g. dilution of a concentrate, reconstitution of liquid medicine, subdivision of a solid dosage form) by health professionals, parents or caregivers prior to administration should ideally be avoided or, at least, kept to a minimum.

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.

Alternatively, the dosage form should be easy to subdivide into smaller, uniform doses of appropriate size, or the intended liquid 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 and 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, 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 influences 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, to increase risk of accidental poisoning. It is preferable that the dosage form is palatable in itself. The caregiver may, however, attempt to improve the ease of administration and acceptance of the patient by mixing the dose with food or beverages, but this should generally not be encouraged.

2.3 Minimum dosing frequency

Parents and caregivers take care of the medication of small 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 are 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 adherence 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 life style of older children.

2.4 End-user needs

In addition to the acceptability and palatability of paediatric medicines it is important that they are affordable. They should be conveniently produced, i.e. feasible to manufacture in good manufacturing practice (GMP) facilities equipped with standard manufacturing equipment, transportable, i.e. low bulk weight and volume, and stable in a variety of climates. Storage in a refrigerator by the user is not always possible.

Depending on age and clinical condition of the patient, 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. Provision of the liquid vehicle as a part of the package may be a solution, or the dose may be dispersed or dissolved in suitable food or beverage prior to administration. Some instructions on such use should be labelled despite the problem that there may be regional and cultural differences with regard to preferred taste.

3. Dosage forms to be considered in particular

- (a) Dosage forms that, in general, are likely to prove most suitable 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 younger age groups, e.g. dispersible and soluble tablets. The flexible dosage form design may be used for several APIs. They may not be suitable for medicines requiring a precise dose titration or molecules that belong to classes 2 and 4 of the biopharmaceutics classification system (BCS) (see section 4.2).

Provided that the medicine can be dispersed in breast milk from the mother, it could potentially be used in very young children (< 6 months).

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. mini-tablets 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).
- (c) For severe disease conditions, e.g. neonatal sepsis, injections are the best existing option. Products with varying vial sizes or strengths to ensure suitability for all age groups are needed, as are packaging options that allow convenient use.

- (d) As an alternative to injections in severely ill children or children unable to swallow, the use of rectal preparations for indications of severe malaria, pain and infection 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 clinical purpose, API properties such as taste, aqueous solubility, pharmacokinetic and pharmacodynamic properties, and stability during manufacture, storage and use of the chosen dosage form [v]. The age, size and condition of the child, e.g. critical illness, co-medication of medicines, 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. FDC products are chosen only when the combination has a proven advantage over single compounds administered separately². FDCs are technically more demanding than single compounds; guidance is provided by WHO³.

4.1 Quality

In the pharmaceutical development of paediatric medicines attention should be paid to current quality guidelines, especially those provided by WHO, e.g. guidelines on development of generic products⁴.

The acceptable level of impurities in APIs and degradation products in finished dosage forms must be qualified and controlled according to regulatory guidelines, e.g. ICH topics Q3A⁵, Q3B⁶ and Q3C⁷. Safety margins established during toxicological studies on an API and finished dosage form usually apply to the worst-case level in adults. Such limits typically apply to both adults and children because a child of lesser weight receives less dose and hence less impurity. However, there are concerns about safety margins for the younger age groups because of the lack of scientific evidence. Term and pre-term neonates have to be considered specifically and may require studies in juvenile animals.

The final product shall comply with the requirements in relevant pharmacopoeia monographs, preferably *The International Pharmacopoeia*. With regard to dissolution testing the appropriate test media may differ from those employed for adult medicines with regard to pH and ionic strength. For dissolution testing of special dosage forms such as chewable tablets,

² WHO Technical Report Series, No. 946 (2007), Chapter 3.3.

³ WHO Technical Report Series, No. 929 (2005), Annex 5.

⁴ Pharmaceutical Development for multisource (generic) pharmaceutical Products (draft working document QAS/08.251/Rev.1).

⁵ ICH Topic Q3A(R2), Impurities in New Drug Substances.

⁶ ICH Topic Q3B, Impurities in New Drug Products.

⁷ ICH Topic Q3C, Impurities: Guideline for Residual Solvents.

suspensions and patches, see the FIP/AAPS guideline for dissolution testing of special dosage forms [vi].

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. A highly soluble API has a dose:solubility ratio of 250 ml or lower at 37°C over the pH range of 1.2 to 6.8. A highly permeable API is absorbed orally to an extent of 85% or more. 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 a WHO Technical Report⁸.

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. As absorption of class 2 substances is limited by dissolution rate effects of particle size, polymorphic form, solubility enhancers, etc., should be considered. The same applies to class 4 substances, though factors other than dissolution govern the oral absorption.

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, the frequency of dosing and acute versus chronic use.

The added challenge for paediatric medicines compared to adult medicines is that excipients in children may lead to adverse effects that are not experienced in adults or not seen to the same extent. Reviews on adverse effects 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 have been reported for benzalkonium chloride, benzyl alcohol, dyes, propylene glycol and sulfites [vii]. 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 [viii]. The toxicity of excipients in newborns and infants can be explained by factors related to the physiological and metabolic development (see reference 1). Information on the safety of some excipients is provided in reviews published by the American Academy of Pediatrics (see “Inactive” ingredients in pharmaceutical products: Update: <http://www.pediatrics.org/cgi/content/full/99/2/268>).

In the development of paediatric medicines, the number of excipients and their level in a formulation should be reduced to a minimum. Toxicological risks are mostly associated with

⁸ WHO Technical Report Series, No. 937, Annex 8.

excipients used for liquid dosage forms, whereas solid dosage forms usually can be formulated by the use of non-toxic excipients.

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; and
- regulatory status in the intended market.

The acceptability of the excipient has to be considered because different cultural or religious reasons mean that some excipients, e.g. gelatin, may not be tolerated. Potential alternatives for excipients imposing a significant risk to the 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 profile are to prefer, new excipients cannot be fully excluded when necessary in innovative products. In any case, the choice of a particular excipient should be based on an assessment of benefits against potential risks.

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 motivated 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 preferable because size, shape and embossing can facilitate identification of different strengths of the preparation. Concerns on the safety of colouring agents in paediatric medicines are associated with reports on hypersensitivity [ix]. 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 for allergic reactions associated with natural colorants [x].

4.5 Antimicrobial preservatives

Medicinal products 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 semisolid preparations and may be needed for other aqueous preparations as well. Usually, solid dosage forms do not need preservation.

Preservatives have a potential to cause toxicological problems, in particular in young children, especially sodium benzoate and benzyl alcohol. The need to preserve and the choice of preservative system should, therefore, be subject to a risk analysis taking into account the target age group and short-term/long-term use. If the risk to benefit balance is critical, a solid dosage form is preferable whenever possible.

Ophthalmic preparations for use in paediatric patients should be prepared without antimicrobial preservatives.

4.6 Sweetening agents

Palatability of oral paediatric medicines often calls for the use of sweetening agents like cariogenic and non-cariogenic sugars and artificial 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 phenylketonurea;
- laxative effect of poorly absorbed or non-digestible sweeteners in high concentrations; and
- the severity of the condition to be treated, i.e. side effects 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 [xi]. Children seem to prefer higher levels of sweetness than adults. The unpleasant taste of an API, e.g. bitterness, is, therefore, often masked in an oral liquid by the use of sweetening agents and flavors. Additional use of colouring agents that match the flavour is discouraged for the reasons stated in 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. [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.

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. Usually non-cariogenic sugars and flavors are used.

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 acceptability 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 comes the fact that gastric emptying of sick newborns is most erratic and can be very much delayed. Further information can be found in an EMA guideline concerning term and preterm neonates [^{xii}].

Oral dosage forms may be mixed with food or beverages to increase child acceptability and ease of administration. Depending on the food or beverage, it may affect the bioavailability and stability of the medicine. If the manufacturer includes such mixing in the product information, the potential effects of food or beverage on stability and absorption should be considered. 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.

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 using 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. Typical target dose volumes are less than 5 ml for children under 5 years and less than 10 ml for children of 5 years and older [^{xiii}]. 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 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.

Solutions

The aqueous solubility of the API may limit the achievable concentration in oral solutions and, hence, the desirable dose volume. In many cases an acceptable liquid formulation requires the use of solubility enhancing methods, i.e. 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.

It is desirable that no ethanol be included in paediatric medicines because the safety implications are not well understood. However, if ethanol is unavoidable, the concentration should be kept as low as possible. The amount of ethanol contained in any medicine should not be able to produce a blood concentration greater than 25 mg/100 ml after a single dose, and appropriate dosing intervals should be prescribed to prevent accumulation of blood alcohol [^{xiv}]. The package volume should be kept to a reasonable minimum to prevent effects of accidental ingestion of the whole contents.

Drops

Some solutions 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 is discouraged because of the inaccuracy in measuring the dose volume and risk for overdosing, which is highly critical in case of potent drugs.

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. Nevertheless, there is a significant risk for dosing errors because of sedimentation and possible caking of the suspension during storage and use.

During manufacture, oral suspensions are submitted to dissolution testing (see reference 6).

Powders and granules for reconstitution

Solid preparations for reconstitution of oral liquids (solutions, suspensions) may be considered when the liquid preparation possesses a short shelf-life due to chemical instability. Powders and granules for reconstitution are usually provided in containers that can hold the reconstituted multidose preparation. The liquid vehicle should preferably be provided together with the dry preparation, especially when the product is intended for markets where access to clean water may be difficult. In many cases, the vehicle is formulated to render the reconstituted liquid stable and palatable.

Granules and freeze-dried preparations are preferable in order to minimize dust problems at the reconstitution. To secure 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 nasogastric tubes

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

Dosing accuracy should be considered taking into account the ease of “extrusion” (viscosity, particle size and amount of suspended components, etc.), potential absorption of API into the tube material and rinsing by flushing of the tube.

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 or dispersion in water or other suitable liquids. The advantages over oral liquid preparations are improved stability, good dosage uniformity, options for different doses and they are easy to administer. They are manufactured by standard equipment and are convenient for packaging and transport.

While powders and multiparticulate preparations mixed with food or beverages may be acceptable from the moment where an infant is able to accept solid food, i.e. about six 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 six years. However, no good scientific evidence exists. Recent preliminary evidence indicates that tablets small enough may be the dosing form preferred even by quite young children.

Powders and multiparticulate preparations

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

Multiparticulate preparations are 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 less than 1.5 mm. In order to ensure dose accuracy, especially when only a portion of the provided dose is administered, it is necessary to use an API with a mean particle size of not more than 5–10 micrometers (i.e. a “micronized” API) and to

perform dose uniformity control 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 non-toxic 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. In addition, pellets and mini-tablets are suited for the platform technology mentioned in section 3b.

Immediate-release tablets

Conventional tablets are uncoated tablets, film- and sugar-coated tablets 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. Every effort to differentiate the appearance of tablets from confectionery should be made.

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 dose units. 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 may crush tablets to increase user-friendliness and compliance. It may, however, affect the bioavailability of some medicines. Thus, 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 preferable.

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 aftertaste. They are usually formulated with a high content of a water-soluble sweetener like mannitol that provides a sweet, cooling taste and good mouth feel, and microcrystalline cellulose, which assists in obtaining a good mouth feel and reduces grittiness. Other sweetening agents like sorbitol and xylitol in technical qualities suited for direct compression are also used.

Chewable tablets are often provided in blister packaging to ensure low moisture content. Chewable tablets may be suited for children of four years and older. A potential problem with chewable tablets is that they may be swallowed by a patient without proper chewing or no chewing at all. It is, therefore, strongly recommended that chewable tablets are formulated so they may be swallowed whole and, thus, labelled – at least in the patient leaflet – 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 [6].

Only tablets that must be chewed should be labelled “chewable tablet”.

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 that the solution should not be drunk before effervescence has subsided in order to minimize ingestion of hydrogen carbonate.

Drawbacks of effervescent dosage forms are the need for clean water for dissolution and the ingestion of potassium or sodium, which makes 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. The need for clean water is a disadvantage. For the convenience of users, the formulations should disintegrate or dissolve within a short time when added to water at room temperature. 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 obtained by 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 would depend on other factors such as the aqueous solubility, intestinal permeability and plasma elimination half-life, which may differ from 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 the variability of these. The same applies to the design of dissolution testing and establishing in vivo-in vitro correlations.

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

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. Hard capsules may be opened and their contents taken as such or taken after mixing with food or sprinkling onto food.

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. There are no restrictions on the amount of API to be incorporated, and the manufacture is made using standard tablet equipment. The product may be moisture-sensitive.

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 [^{xv}]. Oral lyophilisates are sensitive to moisture and require 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 waters may have dissolution times of less than 30 seconds.

Orodispersible and orosoluble dosage forms are attractive for several reasons. They are easy to administer, do not require additional water or other liquids, disintegrate or dissolve quickly, and they are difficult to spit out. They are 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. Alternatively they may be used to prepare oral liquids for younger children.

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.

Orodispersible tablets are flexible dosage forms (see section 3a) suited especially for highly water-soluble APIs.

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 effect (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, palatability issues or significant oral first-pass metabolism. 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, e.g. rectal foams provided in pressurized containers, are available.

When suppositories and rectal capsules are administered to paediatric patients, there is a risk of premature expulsion, especially when the basis has 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 the 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, for example, should be avoided because the majority of suppositories contain the API as solid particles, which may be unevenly distributed in the basis due to by the manufacturing technique by moulding a molten formulation.

Two types of suppository bases are available: (i) insoluble in water, e.g. hard fat, which melts below body temperature; and (ii) soluble or miscible with water, e.g. macrogols, which are dissolved in or mixed with the rectal liquid. Both types may be irritating. Attraction of water from the rectal mucosa by macrogols may be reduced by moistening of the suppository prior to insertion. With both types of bases, consideration has to be given to climatic conditions (temperature) and refrigeration capability.

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 features as formulation of other aqueous liquids, i.e. use of stabilizing agents including surfactants and antimicrobial agents. Non-ionic surfactants are preferable 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 (iv) 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.

Repeated injections should preferably be avoided in children unless they can be given iv via catheters/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 label the size of syringe that permits accurate administration.

Aqueous preparations 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 aqueous solutions intended for iv administration. Isotonicity is highly important and excessive amounts of electrolytes should be avoided (see reference 12).

There are serious constraints on excipients for parenteral preparations. It is highly important to consider the safety profile of each excipient and its suitability for the intended use (see section 4.3).

Consideration should be given to the potential migration of the API into plast containers and catheters, and release of substances from containers 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.

Most children have a fear against injection needles. Possible alternatives, especially suited for frequent or long duration of treatment, are needle-free injection devices, e.g. jet injectors, that drive small droplets through the skin by high pressure. They are used primarily for sc injections.

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). There are used to obtain local effects.

In the development of such preparations for paediatric use consideration must be given to the condition of the skin. In the first years after birth, the state of hydration of the skin and thickness of the stratum corneum are different from those of adults. This means that unintended systemic absorption through the dermis is a potential risk for many APIs.

Dependent on the dosage form, various excipients are needed. The safety profile of each must be considered (see section 4.3), including the risk of sensitizing 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 (see reference 6).

8.1 Transdermal patches

Transdermal patches are used for systemic delivery of APIs which are capable of diffusion through the stratum corneum and are 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 much simpler than the “drug-in-reservoir” type originally

developed; 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 of deliberate removal and its consequences for the 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.

If it is possible to cut the transdermal patch into smaller patches to provide lower doses, this should be labelled. In general cutting is not acceptable because it introduces variability of the released dose.

Adhesives should have a low allergenic potential to avoid irritation and infection.

9. INHALATIONS

Pulmonary administration of medicines by inhalation is used traditionally to obtain a local effect. This route of administration also has 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 [^{xvi}]. 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 the size distribution of the aerosol and patient-related factors like 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 [^{xvii}]. The particle size of the aerosol produced by the delivery device should, therefore, be adapted to children. It has been suggested that the optimal particle size of nebulized aerosols for infants should have an aerodynamic diameter of less than 2.4 mikrometer [^{xviii}].

Nebulizing liquids are important in young children who cannot use MDIs and DPIs. Their uses require, however, nebulizing devices and access to electricity.

MDIs may be applied to 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 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 of 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;
- being robust and convenient for the supply chain, i.e. transportable;
- being tailored to the target age group;
- contribute to in-use stability; and
- 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 to have the product packaging noticeably different between the two products.

Self-administration of medicine in school children 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; and
- clear instructions for use are included.

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.

Adequate information about the medicine and how to use it are important. Drawings or pictograms showing time, method and route of administration are strongly recommended.

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