Annex 5

Development of paediatric medicines: points to consider in formulation

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

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References
1. Introduction

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

The manipulation process itself can increase the potential for inaccurate dosing 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 to underdosing and a resultant reduction in 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 to meet 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 objective is to inform regulatory authorities and manufacturers on issues that require special attention in pharmaceutical formulation. Its focus is on the conditions and needs in developing countries. The guidance does not provide exhaustive information and does not exclude the possibility that other aspects may be relevant to the development of paediatric medicines.

It is not within the scope of this document to address extemporaneous preparations and compounding. A separate interim document entitled Provision by health-care specialists of patient-specific preparations that are not available as authorized products – points to consider (1) will deal with such preparations.
2. Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

*child-resistant container*
A form of 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. may 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 the scope of regulatory authorization.

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

3. Paediatric dosage forms

The paediatric population is a heterogeneous group ranging from newborns to adolescents with wide 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). The age groups identified by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (3) have been derived mainly from physiological and pharmacokinetic differences from birth to adulthood:

- preterm newborn infants
- term newborn infants (0–27 days)
- infants and toddlers (28 days–23 months)
- children (2–11 years)
- 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 risks and benefits taking into account the specific needs of this vulnerable population (4).

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 further enhancement of 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 stages of development within the broader context of quality assurance principles, including the use of quality risk management and pharmaceutical quality systems (4, 5).

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. There is, however, limited information on the acceptability of different paediatric dosage forms in relation to age and therapeutic needs and on the safety of excipients in relation to the development of the child. A European Medicines Agency (EMA) reflection paper on paediatric formulations (6) provides background information on these issues. Reviews by Ernest et al. (7) and Krause and Breitkreutz (8) discuss the needs and challenges in developing paediatric medicines.

The desirable features of high-quality paediatric medicines common to all dosage forms are outlined below. Further information on specific dosage forms is given in the following sections.

3.1 **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 for health professionals, parents or caregivers
to manipulate the dose 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, to enable accurate dosing, the dosage form should be designed to subdivide into smaller, uniform doses of appropriate size and, for liquid forms, the dose volume should be accurately measured.

3.2 Acceptability and palatability

Acceptability is the overall acceptance of the dosage form regardless of the mode of its administration. Acceptability of a dosage form depends on a variety of factors such as:

- suitability of the dosage form for the particular age group
- the dosing device used for a liquid medicine
- palatability of an oral medicine
- dose volume or size to be administered
- appropriateness of packaging
- clarity and accuracy of labelling information
- directions for use.

Acceptance of parents and caregivers is also a relevant issue, and the cultural setting may influence the understanding of and expectations of the therapy.

Palatability is the overall acceptance of the taste, flavour, smell, dose volume or size, and texture of a medicine to be administered by mouth or to be swallowed. Palatability can be crucial to adherence. Palatability of the API may influence the choice of dosage form and its design, which may include taste-masking ingredients. The dosage form should not, however, be made too attractive to the child (e.g. it should not be in the form of a sugar-coated tablet resembling a sweet or candy) in order to avoid increasing the risk of accidental poisoning.

It is preferable that the dosage form is palatable in itself without any need for further modification. The caregiver may, however, attempt to improve the ease of administration and acceptance of the patient by mixing the dose with food or a beverage. Such mixing 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 a beverage (including breast milk) is foreseen, this eventuality 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.
3.3 Minimum dosing frequency

Parents and caregivers take care of the administration of medication to young children, whereas schoolchildren and adolescents can often manage their medication themselves. In both cases minimal dosing frequency should be aspired to. 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 have a negative impact on adherence to the dosing scheme both by caregivers and by older children, in particular when medicines are taken in settings where a trained caregiver is not available, e.g. at school. Moreover, frequent dosing may conflict with the lifestyle of older children.

3.4 End-user needs

In addition to maximizing 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. It is not always possible for the user to store medicines in a refrigerator.

Depending on the age and clinical condition of the child, there are restrictions to the applicable dose volume or size. Generally, when developing the product, minimum dose volume and size should be the goal.

Lack of access to clean water is an important issue to take into consideration in the development of medicines that need 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. by supplying instructions on boiling or filtering. Provision of the liquid vehicle as a part of the package may be an option, or the dose may be dispersed or dissolved in a suitable food or beverage prior to administration. Some instructions on such use should be included on the label or package insert. Regional and cultural differences with regard to preferred tastes may need to be considered.

4. Particular dosage forms to be considered

4.1 Flexible solid dosage forms

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 but 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 taken into account, as unpleasant tasting medicine may cause aversion in breastfed children. In addition, the compatibility of the API with breast milk will need to be considered. The same considerations apply 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 to ensure that package sizes will allow optimal use under public health programmatic conditions.

4.2 **Oral medicines**

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 to be sprinkled onto food. Platform technology has potential flexibility for manufacturing appropriate fixed-dose combination products (FDCs). Breakable solid dosage forms specially designed to provide the appropriate dose may also serve the same purpose (1, 9).

4.3 **Medicines for severe conditions**

For severe disease conditions, e.g. neonatal sepsis, the use of alternative dosage forms should be carefully considered. Some alternatives may be easier for untrained caregivers to administer, e.g. a 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.

4.4 **Rectal preparations**

As an alternative to parenteral preparations for severely ill children or children who are 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.

5. **Formulation design**

When designing paediatric medicines, the route of administration, dosage form and dose of the API are 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 \((10)\). The age, size and condition of the child (e.g. critical illness, concomitant medication, or inability to swallow a dose), 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 separately, for example, to achieve compliance in multidrug regimens for treating human immunodeficiency virus (HIV) and/or tuberculosis (TB). The development of FDCs may be more complex than for single compounds; guidance is provided in WHO guidelines \((11)\).

5.1 Quality
In the pharmaceutical development of paediatric medicines attention should be paid to current quality guidelines, especially those provided by WHO \((1)\).

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 \((12–14)\). Safety margins established during toxicological studies on an API and finished dosage form usually apply to a worst-case level in adults. Such limits typically apply to both adults and children; although a child would receive a smaller dose, the exposure per kilogram is likely to be similar. Term and preterm neonates have to be considered specifically, and establishment of safety limits may require safety studies in juvenile animals. Additional guidance may be found on the EMA website \((15–17)\).

The final product should comply with the requirements in relevant pharmacopoeial monographs, preferably those in \textit{The International Pharmacopoeia}\(1\). With regard to dissolution testing, dissolution media should be carefully reconsidered in view of the different gastric pH of children from that of adults. Testing at other pHs should be considered in relevant cases. For dissolution testing of special dosage forms, such as chewable tablets, suspensions and patches, see the International Pharmaceutical Federation/American Association of Pharmaceutical Scientists (FIP/AAPS) guidelines for dissolution testing of special dosage forms \((18)\).

5.2 Biopharmaceutics classification system
The biopharmaceutics classification system (BCS) is a scientific framework for classification of APIs for oral administration. The BCS is based upon aqueous

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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 1.2–6.8. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a medicine together with a glass of water to fasting human volunteers. 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 (19).

Hence an API can be classified as belonging to one of four classes:

- class 1 (high solubility, high permeability);
- class 2 (low solubility, high permeability);
- class 3 (high solubility, low permeability);
- 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 (20).

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 a 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, and solubility enhancers, among others, should be considered, as the absorption of these substances may be limited by dissolution rate. The same applies to class 4 substances, although 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 the dosage form and/or excipients used in adult medicines differ from those used for paediatric medicines.

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

5.3 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 factors such as the paediatric age group, frequency of dosing and duration of treatment.

The added challenge for paediatric medicines compared to adult medicines is that excipients may lead to adverse reactions in children that are
not experienced by adults or are not seen to the same extent. Reviews of the literature on adverse reactions attributed to excipients show that the available data on excipient safety are limited in quantity and variable in quality.

Major problems with excipients in paediatric medicines, especially when used to treat infants and neonates, have been reported (21), e.g. medicines with benzyl alcohol, azo-dyes, propylene glycol, ethanol and propyl paraben. A study on the exposure to benzyl alcohol and propylene glycol of neonates receiving parenteral medication demonstrated a potential risk of toxic doses, especially for neonates receiving continuous infusion (22). The toxicity of excipients to newborns and infants can be explained by factors related to their physiological and metabolic development (2). Information on the safety of some excipients may be found, for example, in reviews published by the American Academy of Pediatrics (23). Alternative sources of information should also be consulted, e.g. the WHO Technical Report Series on Evaluation of certain food additives (24).

In the development of paediatric medicines, the number of excipients and their quantity 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 necessary 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;
- the 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 which pose a significant risk to children should always be considered. Another dosage form or even a different 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 their safety, quality and appropriateness for use in children have been established. It may also be necessary to look at alternative excipients because of different cultural attitudes or for religious reasons, e.g. the use of gelatin may not be acceptable for all patients.
5.4 **Colouring agents**
The use of colouring agents in paediatric medicines is generally discouraged, in particular in medicines 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.

Some colouring agents used in paediatric medicines have been associated with hypersensitivity (25). The number of colouring agents that are acceptable for use in medicines is limited. Azo-dyes should be avoided in children’s medicines and attention should be paid to the risk of allergic reactions associated with natural colourants (26).

5.5 **Antimicrobial preservatives**
FPPs may require antimicrobial preservatives to avoid microbial proliferation during storage, in particular under in-use conditions. Preservatives are 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 require preservatives.

Preservatives may have a potential to cause adverse reactions, in particular in infants and neonates, and should be avoided where 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, their concentration should be 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 (27) published on the EMA web site.

5.6 **Sweetening agents**
Oral paediatric medicines often use sweetening agents to make them palatable. These may be either cariogenic or 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, and avoiding 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 adherence?

5.7  **Taste masking**

Taste masking in medicines for oral use or for 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. They are able to recognize sweetness and saltiness from an early stage and are also able to recognize a sweet taste in oral liquids and the degree of sweetness (28). Children seem to prefer sweeter tastes than adults do. The unpleasant taste of an API, e.g. bitterness or a 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 this is necessary to disguise an unpleasant colour related to the API. Some successful approaches to taste masking are discussed by Ernest et al. (7).

A child’s preference for particular flavours is determined by individual experiences and culture. The target for taste masking need not necessarily be good-tasting medicines; it should simply be a taste that is acceptable in as many countries as possible taking into account cultural differences.

An example of a “qualitative evaluation of the taste by a taste panel” for zinc formulations can be found in the United Nations Children’s Fund (UNICEF)/WHO publication on production of zinc formulations (29, 30).

Consideration should be given to the items listed in sections 4.3 and 4.6.

Taste masking for orodispersible tablets and chewable tablets is in principle similar to taste masking for oral liquids. Non-cariogenic sweeteners and flavours are preferred.

5.8  **Solubility enhancers**

The aqueous solubility of the API may limit the concentration achievable in formulated solutions and, hence, the desirable dose volume. In many cases an acceptable solution requires solubility enhancing methods, e.g. use of non-ionic surfactants and of co-solvents such as glycerol, liquid macrogols and ethanol. If solubility enhancers are to be used, consideration should be given to the safety of both the agent and the formulation, for example, the 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 they are included in parenteral preparations than when used in oral preparations.

Ethanol, especially in large amounts, should not be administered to children (aged 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 possible amount should be used. When ethanol is used, adequate development data demonstrating that the lowest possible concentration of ethanol is used should be established.

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

6. Oral administration

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

Consideration should be given to the effects of increased gastric pH and intestinal mobility at birth and in early infancy (2). In addition, gastric emptying of sick newborns is most erratic and can be delayed. Further information can be found in an EMA guideline on medicines for term and preterm neonates (31).

Mixing oral dosage forms with food or a beverage is not recommended, 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, attention should be paid to the effect on the taste, as an unpleasant taste of medicine may cause aversion in children.

6.1 Oral liquid preparations

Oral liquid preparations include aqueous solutions, suspensions, emulsions and syrups. They are most appropriate for children in the youngest age groups who 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 stabilizing agents, e.g. antimicrobial preservatives, is a major drawback as is the potential chemical instability, which may lead to a requirement for controlled storage
conditions during distribution and use. Oral liquid preparations are less transportable than solid-dose preparations because of their relatively high bulk volume.

The dose volume is important for the acceptability of the preparation. High-dose volumes pose a risk of incomplete ingestion and, thus, underdosage. Efforts should, therefore, be made during pharmaceutical development to minimize the dose volume while recognizing the need to ensure 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 (32). There is some uncertainty about these limits because the more palatable the formulation, the higher the dose volume that 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 preservatives. Special attention has to be paid to the in-use stability of multidose preparations, both microbial and physicochemical.

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 other devices such as graduated pipettes or plastic spoons. 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 correct dosing is 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 the dose is swallowed. The use of this dosage form should be evaluated using a risk-based approach to ensure it is suitable given the medicine’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 in some instances be a significant risk of 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 (18) unless otherwise justified.

**Powders and granules for reconstitution**

Solid preparations for reconstitution as solutions or suspensions should be considered, especially when the liquid preparation has a short shelf-life due to instability (chemical, physical or microbiological). Powders and granules for reconstitution are produced as 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 ensure their proper use, the solids must be easily wetted and dispersed or dissolved within a short time once the vehicle is added.

The major drawbacks of this type of formulation are the bulk volume of the preparation, i.e. it is 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 3.1 are preferable.

### 6.2 Administration through feeding tubes

For 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 its bioavailability.

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

These considerations should be highlighted in the SmPCs.

### 6.3 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 or orodispersible tablets). Some are
intended for swallowing after dissolution, dispersion in water or other suitable liquids. Their 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. These forms are convenient for packaging and ease of 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 at which intact tablets and capsules are acceptable. It has been thought generally that even small tablets and capsules to be taken whole are not acceptable for children below the age of 6 years. However, no good scientific evidence exists to support this notion. Recent preliminary evidence indicates that mini-tablets (with a diameter of less than 4 mm) may be acceptable even by the majority of small children (2–4 years old) (33).

**Powders and multiparticulate preparations**

Powders and multiparticulates are provided in sachets or in hard capsules that allow the contents to be taken directly or after manipulation, e.g. following 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, which produces uniform particles within the size range 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. Control of dose uniformity should be performed on a level corresponding to the dose to be taken by the target age group.

Multiparticulate preparations offer 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 an appropriate number of pellets or mini-tablets. A counting device may be necessary when a large number of pellets or mini-tablets is required. In addition, pellets and mini-tablets are suited for the platform technology mentioned in section 3.2.

**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 resemble
sweets or candies and hence may be too attractive to the child. It is critical to
differentiate the appearance of tablet packs from that of confectionery packs.

Break-marks intended to enable accurate subdivision of the tablet to
provide doses of less than one tablet should be proven to result in 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*
(34). 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.

Caregivers often crush tablets to increase user-friendliness and
adherence. Crushing 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.

Tablets should not be crushed unless instructions allowing crushing
are provided on the label by the manufacturer. Generally a multiparticulate
formulation supplied in sachets, hard capsules or blister packs 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 they should not leave a bitter
or unpleasant aftertaste. They are usually formulated with a high content of a
water-soluble sweetener, such as mannitol, which 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 before being properly chewed or without being chewed at all. It is,
therefore, strongly recommended that chewable tablets are formulated so that
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 should 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 their non-disintegrating nature it may be necessary to alter the test
conditions (18).
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 given on the label. Furthermore, the label should give instructions that the solution is not to be drunk before effervescence has subsided, in order to minimize ingestion of hydrogen carbonate. Effervescent tablets require continuous attention to levels of moisture and humidity during manufacture, packaging and storage.

The 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 to be used in the same way as effervescent tablets. Their advantage is that problems with hydrogen carbonate, potassium and sodium are avoided. For the convenience of users, the formulations should disintegrate or dissolve within a short time of being added to water. It is helpful when an indication of the minimum volume of water is provided on the label.

Dispersible and soluble tablets are flexible dosage forms, the formulation of which may be suited for several water-soluble APIs (see section 3.1).

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 formulations, e.g. as 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, a feature which may improve adherence (see section 2.3). Not all APIs can be formulated as sustained-release products. This will also depend on other factors such as aqueous solubility, intestinal permeability and plasma elimination half-life, which may differ between children and 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 and their variability, e.g. gastric pH and emptying rate and intestinal mobility.

The majority of sustained-release formulations, especially coated tablets and matrix tablets, must not be broken or chewed and some will not withstand being mixed with food or a beverage. It is, therefore vital that clear instructions on the proper use of the formulation are included on the label.
Capsules
Capsule formulations are provided either as soft capsules, usually with a liquid or semi-solid content or as hard capsules containing powder or a multiparticulate formulation.

Capsules may be taken whole. The limitations mentioned for tablets apply with regard to the ability of the child to swallow them (see introduction to 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 provided on the label, e.g. whether the capsule has to be taken whole or whether the capsule contents can be mixed with food to facilitate intake and improve 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, after which the dose is swallowed.

Orodispersible tablets designed to disintegrate rapidly 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 its physical properties. The product may be moisture-sensitive. Orodispersible tablets are flexible dosage forms (see section 3.1), particularly well-suited 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, which act as structure-forming agents, and mannitol, which facilitates formation of the porous structure and contributes to palatability. Instead of mannitol, sorbitol may be used as a crystallization inhibitor. The amount of water-soluble API to be incorporated is limited (35). 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 using water-soluble sweeteners and flavourings.

7. Rectal administration

Rectal administration is an important route 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. This 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 unpredictably 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 premature infants, as they can tear very delicate tissues and, thus, introduce infection.

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

7.1 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 as a result of the manufacturing technique of moulding a molten formulation. However, it is also possible to prepare suppositories which can be cut in smaller portions, ensuring delivery of an 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 base are available: one is insoluble in water, e.g. hard fat, which melts below body temperature. With suppository melt formulations, special consideration has to be given to storage temperature. The
other type of suppository is soluble or miscible with water, e.g. macrogols, which are dissolved in or mixed with the rectal liquid. Both types may be irritants.

7.2 Rectal liquids (enemas)
Rectal liquids are solutions, suspensions or emulsions based on water or vegetable oil. Any volume to be administered should be appropriate 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 to avoid 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 is similar to the formulation of other aqueous liquids regarding 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.

8. Parenteral administration
Parenteral administration by the intravenous route is preferred for seriously ill children and for clinically unstable term and preterm neonates (in developed country settings). Some parenteral preparations are administered by the subcutaneous and intramuscular routes. The limited muscle mass of newborns and, in particular of preterm infants, constrains the use of intramuscular 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 children undergoing frequent or long-duration 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 subcutaneous administration. However, experience of their use in paediatric populations, especially in smaller children is limited.

Repeated injections should be avoided for children unless they can be given intravenously via catheter or 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 taken into account.

Age- and weight-related preparations (injection volume and strength) are preferred in order to provide an acceptable injection volume, and to avoid dosing errors due to improper use of multidose preparations and errors in calculation of the dilution required to obtain measurable volumes. It is helpful to state 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.

8.1 **Formulation**

Aqueous preparations (solutions or 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, subcutaneous 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 intravenous administration. Target volumes and electrolyte contents are important for all paediatric patients; however, these are critical for neonates (19).

It is crucial to consider the safety profile of each excipient and its suitability for the intended use (see section 4.3).

Attention should be paid to the potential adsorption of the API on to the surfaces of plastic containers and catheters, and to leaching of plasticizers from containers and catheters to the parenteral preparation.

Some APIs are presented as powders or lyophilisates to be reconstituted before administration. It is important that clear instructions on the reconstitution and information on storage conditions and duration appear on the label or product information.

8.2 **Additional points to consider for parenteral preparations**

- There should be a minimal need for complex calculations for prescribing, dispensing and administration (e.g. dose in micrograms/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 percentage concentration on the label; and decimal points).
- The need for additional steps in the preparation of the product for administration should be minimized, for example, by developing ready-to-use preparations.
- Measurement of volumes smaller than 0.1 ml should not be required. Dose volumes in hundredths of a millilitre should be avoided. Tables should be included in the product information clearly stating the dose and the 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 administration of 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 measures and restrictions on administration via central or peripheral cannula should be provided, including advice on maximum and minimum dilutions for safe administration.

- Consideration should be given to the 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 plan should be investigated.

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

9. Dermal and transdermal administration

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

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

Depending on the dosage form, various excipients are needed. The safety profile of each must be considered (see section 4.3) including the risk of sensitization of 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 (18).
9.1 Transdermal patches

Transdermal patches are used for systemic delivery of APIs which are capable of diffusion through the stratum corneum and are therapeutically active at the low plasma concentrations that can be achieved. The manufacture of transdermal patches of the “drug-in-adhesive” type is now well developed and less problematic than the earlier “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 fit 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 chosen to avoid removal of the patch by the child. The risk of 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 cutting 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.

10. Inhalations

Pulmonary administration of medicines by inhalation has traditionally been used 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 the physiology of children of different ages and their ability to use the devices correctly should be considered in the development of paediatric inhalations (8). Depending on their age, children may have more or less difficulty 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 medicine 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 diameter of the airways is smaller in children than in adults; hence deposition by impact in the upper and central airways may be significantly higher in children (36). The particle size of the aerosol produced by the delivery device needs to be explored during development.
Nebulized liquids are potentially suitable for young children who cannot use MDIs and DPIs. Their use, however, requires 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 for children from the age of 4–5 years, as minimum inspiratory flow is required. DPIs and MDIs are preferred for older children because of their portability and convenience.

11. 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 to ensure that they:

- permit accurate dosing and convenient administration;
- are robust and convenient for the supply chain, i.e. transportable;
- are tailored to the target age group;
- contribute to in-use stability;
- provide 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 noticeably different product packaging for the two products. It is necessary that consideration be given to whether the medicine is to be packed in a child-resistant container, i.e. a packaging that is difficult for young children to open, but not unduly difficult for adults to open properly.

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

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

Adequate information about the medicine and how to use it is 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.

References


**Web sites**

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