Annex 8

Development of paediatric medicines: points to consider in formulation

Contents

Abbreviations

AAPS	American Association of Pharmaceutical Scientists
API	active pharmaceutical ingredient
BCS	Biopharmaceutics Classification System
DPI	dry powder inhaler
FIP	International Pharmaceutical Federation
FPP	finished pharmaceutical product
GAP-f	Global Accelerator for Paediatric Formulations
HIV	human immunodeficiency virus
MDI	metered-dose inhaler
PERA	Paediatric Excipient Risk Assessment
PQPPAT	paediatric quality product profile assessment tool
StdC	standard concentration
STEP	Safety and Toxicity of Excipients for Paediatrics
WHO	World Health Organization

1. Introduction

This document aims to highlight areas of specific attention when developing medicines for children. General regulatory principles of quality for the development of medicines should be followed.

Safe and effective pharmacotherapy for the paediatric population requires the availability of and access to age-appropriate medications and accurate information for correct prescribing and administration. These considerations should take into account the child's age, physiological condition and body size. Specifically developed formulations (authorized and suitable for these age groups) are often necessary.

Due to the lack of age-appropriate formulations, pharmacists, health care professionals, parents and caregivers often need to manipulate an adult medicine in a way that is not described in the product information. This manipulation may include breaking, crushing or cutting tablets, as examples. The challenges and potential risks associated with manipulating dosage forms for children have been documented over many decades (*1*).

Such practice may be potentially hazardous for the patient, as it may affect the stability, bioavailability and accuracy of dosing of a finished pharmaceutical

product (FPP). The use of these modified medicines may expose children to the risk of overdosing and unintended side-effects or underdosing leading to reduced efficacy. Additionally, health care providers may face risks, such as exposure to toxic substances, for example, when handling cytotoxic drugs and inhaling powders released from crushing tablets. An additional factor might be the bad taste of the manipulated FPP, which can lead to non-compliance of the child taking the medicine as chronic or daily treatment.

In December 2007, the World Health Organization (WHO) launched its initiative "Make medicines child size" (*2*) in order to raise awareness and to accelerate action to meet the need for improved availability of and access to child-specific medicines. At the same time, the WHO Model List of Essential Medicines for Children was launched to guide countries on the selection of the medications considered to be most effective and safe in children, with regular review every two years (*3*).

Building on these efforts, and following the 2016 World Health Assembly resolution on promoting innovation and access to quality, safe, efficacious and affordable medicines for children (*4*), the Global Accelerator for Paediatric Formulations (GAP-f) was conceived and launched in 2020 as a WHO network to build on and formalize a sustainable mechanism that ensures that safer, more effective and more durable paediatric formulations are developed and made available to children more quickly through an accelerated process or on an accelerated timeline (*5*). GAP-f has membership across 33 organizations, working to establish a prioritized paediatric product portfolio across a product life cycle.

In 2024, at the Seventy-seventh World Health Assembly, Member States recommitted to paediatric medicines and, in resolution WHA77.5 – "Accelerate progress towards reducing maternal, newborn and child mortality in order to achieve Sustainable Development Goals targets 3.1 and 3.2" – specifically called for renewed efforts and appropriate financing to accelerate investigation, development and introduction of better medicines for children (*6*, *7*).

Taken together, these growing efforts are a testimony to the commitment of global stakeholders to address the paediatric medicines gap and the desire to generate sustainable change to allow more equitable access to medicines for all in need.

The objective of this document is to inform regulatory authorities and manufacturers on issues that require special attention when developing pharmaceutical formulations for paediatric use. It covers points to consider for global development of paediatric formulations, including 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.

Sustainability aspects should be considered in paediatric formulation development to support environmentally responsible practices. Initiatives such

as the United Nations Global Compact can provide a structured framework for addressing material sustainability risks and aligning operations to internationally recognized environmental, social and governance benchmarks.

Furthermore, it is not within the scope of this document to address extemporaneous preparations and compounding. A separate guidance entitled *FIP–WHO technical guidelines: points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products addresses such preparations* (8).

2. Glossary

acceptability. Overall ability and willingness of the patient and caregiver to use and administer the medicine as intended. This encompasses factors such as palatability, swallowability, tolerance and user-friendliness, and applies to all modes of administration (oral, rectal, parenteral and topical routes).

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

age-appropriate. Descriptive of medical products that are suitable for the targeted age groups in paediatric populations, indicating dosage forms that are acceptable to and consistent with the general growth and maturation characteristics of the individuals within the respective age bands.

fixed-dose combination. A combination of two or more active pharmaceutical ingredients in a fixed ratio of doses in a single dosage form. This term is used generically to mean a particular combination of active pharmaceutical ingredients irrespective of the formulation or brand.

flexible dosage form. A dosage form where a single unit strength or its multiples may be administered or given to the targeted population for achieving the intended therapeutic dose and effect. This includes the ability to achieve a range of doses (for example, to accommodate patients of different ages or body weights) with a single product, strength or presentation. Flexible dosage form may also refer to a solid dosage form that can be administered to patients in more than one manner, for example, dispersed or taken orally as a whole.

medicine. Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view

to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings. In this document, the terms medicine and finished pharmaceutical product are used interchangeably.

orally disintegrating (orodispersible) dosage form. A solid dosage form intended to be placed on the tongue, where it rapidly disintegrates in saliva without the need for water, forming a swallowable dispersion or solution.

palatability. The overall appreciation of a medicinal product in relation to its taste, smell and texture, which significantly influences adherence in paediatric populations.

For other definitions, please refer to the *WHO Quality Assurance of Medicines Terminology Database*: https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database.

3. General principles

The paediatric population is a heterogeneous group ranging from newborns to adolescents with wide physical and developmental differences affecting the pharmacology of medicines. Organ maturation, metabolic capacity, tissue and receptor maturation, and other factors, such as development, may change with age, especially in early infancy (*9*). There are different definitions and classification for age groups (*10*, *11*).

However, the choice of formulation for the paediatric population is guided by factors not necessarily aligning with age classifications, such as the medical condition and dose, as well as acceptability of the dosage form. Therefore, the decision on the appropriateness of a formulation, and consequently any potential need for other formulation options, might need to be considered independently of age categories.

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 dosage form, including through the development of formulations that provide flexible dosing. This may involve innovative approaches for safe and effective administration, including education and training initiatives, which may improve the acceptability of specific dosage forms by patients and carers. The guiding principle for selecting paediatric dosage forms should be the same as for adults: achieving a balance between risks and benefits while considering the specific needs of this vulnerable population.

The current use of medicines for the paediatric population reflects the full range of dosage forms and routes of administration used for adult medicines; established pharmaceutical development principles can therefore be followed (*12*, *13*). Limitations, however, exist to the acceptability of different dosage forms

in relation to age and therapeutic needs, as well as to the safety of excipients in the context of neonatal and paediatric development, as outlined in various regulatory guidelines (*14*, *15*).

The WHO paediatric quality product profile assessment tool (PQPPAT) provides a framework for assessing the age-appropriateness and suitability of paediatric medicines (*16*). The PQPPAT focuses on dose and dose flexibility, patient acceptability, excipient safety, and administration considerations, as well as stability, storage conditions and primary packaging materials. The desirable features of high-quality paediatric medicines common to all dosage forms are outlined below.

3.1 Administration aspects and end user needs

The administered dose should be accurate for the age and condition of the child. The implication is that more than one dosage form of the active pharmaceutical ingredient (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 and the dose range, where this cannot be avoided and in this case any necessary manipulation should be described clearly and unambiguously in the product information.

Dosing frequency might affect treatment adherence. Although primarily based on the pharmacokinetic and pharmacodynamic properties of the API, dosing frequency may be adjusted by dosage form design. Frequent dosing (for example, more than twice daily) may have a negative impact on adherence to the dosing scheme both by caregivers and by children, in particular when medicines are taken in settings where a trained caregiver is not available (for example, at school), and may conflict with the lifestyle of older children. Minimal dosing frequency through product design should be aspired to whenever possible (for example, consideration of the development of sustained release systems).

Paediatric medicines should be affordable and factors that may influence the supply chain (such as ease of transportation and storage) or access to refrigeration at health care facilities and by users should be considered as part of drug development programmes.

Lack of access to clean water is an important issue to consider 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, for example, 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.

3.2 Acceptability

Acceptability is the "overall ability and willingness of the patient to use and its caregiver to administer the medicines as intended", regardless of the mode of its administration (*14*). It is essential that the formulation and dosage form chosen for the paediatric population is acceptable and appropriate for the target age to ensure adherence to and compliance with treatment.

Acceptability is influenced by factors related to both the product and the user, the condition to be treated, and the cultural setting. It includes aspects such as palatability, swallowability and tolerance. It is a multifaceted concept and depends on a variety of product characteristics, such as volume, size and shape, taste, smell and texture, dosing and administration device, needle size, handling complexity, labelling information and packaging. More information relevant to specific forms and routes is being addressed in later sections.

Considerations regarding patient acceptability should be an integral part of the pharmaceutical and clinical development. Early focus on the appropriateness of the formulation for the target age group is essential, since a poorly acceptable formulation might also affect the outcome of a paediatric trial.

Assessment of acceptability may be requested as part of clinical trials in children, to give reassurance that the medicine is suitable for the targeted paediatric population. Different methodologies can be used to assess acceptability in the paediatric population, for example, through appropriately tailored questionnaires or preference studies, or through more advanced modelling-based methods (*17*–*20*). In-depth assessment of non-compliance during clinical trials could also provide useful insight into acceptability. For the assessment of taste, as an important attribute related to acceptability, supportive data can be gathered from literature data, from adult panels, or from non-human sensory studies (for example, "electronic tongue" or rodent brief-access taste aversion models).

Acceptability considerations have driven the development of in vitro methods suitable for determining the properties of oral dosage forms, such as their mouthfeel, texture, taste and swallowability. In food engineering, technology such as rheology and tribology are being used for understanding the oral processing of food (and beverages when applicable) as well as determination and optimization of its mouthfeel and texture. In vitro techniques have been evolving since the 1960s and, with the use of electronic sensors (for example, "electronic tongue"), taste and taste-masking attributes of the formulations may also be determined, depending on the API and formulation characteristics. Furthermore, for taste masking, non-sensory analytical methods may be of

use (for example, dissolution testing) in combination with bitterness threshold data. Overall, the in vitro technology utilized in the food industry can be a viable platform for characterizing mouthfeel, texture, taste and swallowability of paediatric formulations, providing supportive guidance during development of paediatric oral formulations and further validation as part of the clinical trial (*21*–*28*). Adult panels can also be considered as an alternative for taste assessment in specific cases.

It is the manufacturer's responsibility to ensure that a formulation is age-appropriate from the start of drug product development. In case of concerns that the formulation is not fully appropriate, alternative strategies (for example, lower dilution volumes, crushing and dispersing tablets, opening capsules or tablet splitting) should be envisaged by the applicant and necessary data to support such strategies should be presented.

For generics, it is important to ensure that characteristics related to acceptability are taken into account (*29*).

More details and recommendations regarding acceptability of the different specific dosage forms are addressed in section 5.

3.3 Information and education resources

Organizations dealing with paediatric and neonatal patients in different parts of the world make attempts to overcome the historical lack of information on medicinal products for children with practice advice at the end user stage. Some of their initiatives are useful feedback tools for drug developers, as they could refer to these to further enhance their product design and clinical development (for example, when planning acceptability studies) and product information.

As an example, The Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacy Group in the United Kingdom of Great Britain and Northern Ireland – Medicines for Children partnership developed medicines information resources for licensed and unlicensed medicines relevant to the safe administration of medicines for children and supplementary to product information (for example, with pictograms for the safe utilization of medical devices). These are tested resources and are readily available for health care professionals, parents, carers and children to access (*30*).

Other work being adopted in clinical practice by health care facilities running paediatric clinics and used as part of clinical trial design is the so-called Pill School, enhancing the acceptability of capsules and tablets. Canada and the United Kingdom have conducted research on the benefit of teaching swallowing techniques to children, leading to positive results in compliance with oral solid dosage forms and the reduction of liquid formulation needs (*31*–*34*). These practices should not prevent manufacturers from making every effort to address the need for age-appropriate formulations in their development plans,

but they could support development plans where age-appropriate formulations (for example, oral granules, minitablets, or liquid or dispersible formulations) are not achievable.

Overall, the manufacturer should ensure that precise and clear information on the administration method is provided as part of the summary of product characteristics and product information (including e-product information) to facilitate a clear understanding at end user level, so the medicinal product is administered as intended in the design. The use of electronic product information is encouraged, as it can provide access to further information resources such as videos.

4. Formulation design, paediatric considerations

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, excipients required and stability during manufacture, and storage and use of the chosen dosage form (*35*). The age, size and condition of the child (for example, critical illness, concomitant medication or an inability to swallow a dose) and the expected frequency of administration and duration of the therapy must be taken into account. The selection of the most appropriate dosage form is, therefore, based on case-by-case considerations.

Fixed-dose combinations are chosen when the combination has a proven advantage over single compounds administered separately, for example, to achieve adherence in multidrug regimens for treating human immunodeficiency virus (HIV) or tuberculosis. Fixed-dose combinations available as pellets or scored tablets provide the advantage of dose flexibility. The development of fixed-dose combinations may be more complex than for single compounds; guidance is provided in WHO and other guidelines (*36*, *37*).

4.1 Quality

In the pharmaceutical development of paediatric medicines, attention should be paid to current quality guidelines (*8*, *12*, *13*).

Organic impurities, inorganic impurities, residual solvents, heavy metals and other types of impurities (including biological or microbiological) should be qualified, controlled and defined by their acceptance levels. Safety margins established during toxicological studies on an API and finished dosage form 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 specifically considered and the establishment of safety limits may require safety studies in juvenile animals.

The final product should comply with the requirements in relevant pharmacopoeial monographs, preferably those in *The International Pharmacopoeia* (38).

In vitro release testing

Guidance on dissolution testing has been outlined by the ICH (39), and further recommendations for dissolution testing of special dosage forms, including chewable tablets, orally disintegrating tablets, suspensions and patches, have been provided by the International Pharmaceutical Federation/American Association of Pharmaceutical Scientists (FIP/AAPS) (40). When dosage forms come with labelling instructions for optionally using soft foods and liquids to aid their administration, dissolution drug release testing of the dosage form mixed with the proposed vehicle should be conducted, as well as compatibility and stability (41).

4.2 Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) is a scientific framework for the classification of APIs for oral administration. The BCS is based upon aqueous solubility and intestinal permeability.

An API is considered highly soluble when the highest dose is soluble in 250 millilitres (mL) or less of aqueous media at 37 °C, over the physiological 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. Permeability can also be demonstrated using in vitro methods with Caco-2 cell systems or any other reliable justifiable system. An API can be classified as belonging to one of four classes: BCS class I (high solubility, high permeability), BCS class II (low solubility, high permeability), BCS class III (high solubility, low permeability) or BCS class IV (low solubility, low permeability) (42, 43).

The BCS scheme has been utilized for waiving in vivo bioequivalence studies for specific immediate-release drug products containing highly soluble drugs for adult populations (BCS-based biowaivers) (43). It also provides value in drug characterization during different stages of drug product development to identify formulation approaches for optimizing drug bioavailability. It is important to recognize, however, that drug permeability and solubility considerations for adult BCS may not directly apply to paediatric populations, and bridging of adult and paediatric formulations should be approached on a case-by-case basis. Furthermore, BCS-based biowaivers cannot simply be extended from adult to paediatric populations. Volume and composition of gastrointestinal fluids can vary significantly between adults and paediatric populations (44, 45). Fasting

gastric volumes are lower in children compared to adults, and a 250 mL volume will not be consumed by most children during drug administration. Medicines in the paediatric population are also frequently coadministered with juices, soft foods or full-fat milk. This must be properly assessed as part of development considering that lipid composition, pH and ionic strength may impact drug solubility and stability.

4.3 Excipients

The selection of excipients with appropriate safety and tolerability can be a major challenge in paediatric formulation development. Safety concerns have been reported for excipients in paediatric medicines, especially when used in infants and neonates, where toxicity of excipients can be explained by factors related to their physiological and metabolic development (including renal and liver immaturity) (*9*) as well as disease and co-medications. Severe outcomes have been reported for excipients such as benzyl alcohol, propylene glycol and ethanol, but discussions on safety have also taken place for other excipients, such as azo dyes and propylparaben. Of note, the majority of cases that have triggered safety discussions on excipients result from unacceptable exposures to young children, and the information available needs to be assessed in the specific context. Inclusion of these excipients may be necessary in some cases but all excipients should have favourable risk assessment with adequate margins of safety, and be assessed as part of the overall benefit–risk of the product.

In the development of paediatric medicines, the selection of excipients needs to be justified, as well as 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 quality. The use of an excipient in previously authorized drug products should not set a precedent, as it may not be appropriate for use in different paediatric subpopulations.

The daily and cumulative excipient dose (milligrams per kilogram per day (mg/kg/day); mg/kg/treatment period) and rate of administration (especially intravenous administration) should be carefully considered. The choice of excipients should be justified through a risk-based assessment, and consideration should be given to:

- the safety profile of the excipient for the target age group;
- the route of administration;
- the single and daily dose of the excipient;
- severity of the condition;
- duration of treatment;

- acceptability for the intended paediatric population;
- the role of the excipients and potential alternatives;
- if using two or more excipients with similar risks, the total added risk needs;
- regulatory status in the intended market.

Information on the safety of excipients can be found in resources such as the Safety and Toxicity of Excipients for Paediatrics (STEP) database (46, 47) and the *Handbook of pharmaceutical excipients* (48). Information and recommendations regarding intake are also available from food authority sources (for example, food legislation); however, it should be kept in mind that such recommendations are valid only for the oral route, and often reflect lifelong intake and a potentially different benefit–risk setting than for medicines. Guidelines such as those of the European Commission on *Excipients in the labelling and package leaflet of medicinal products for human use* give specific recommendations on how safety information of excipients should be reflected in the product information, including published reports on some specific excipients, for example, ethanol, methyl and propyl paraben, sodium benzoate, propylene glycol and benzyl alcohol (47, 49–55).

For many excipients, however, the limited safety data available, particularly related to the younger age groups, is a concern, and often makes clear recommendations challenging. An evidence-based approach should be followed based on all available clinical and nonclinical data. Tools are being developed to systematically assess excipient exposure risks in different paediatric age groups, for example, Paediatric Excipient Risk Assessment (PERA) (56, 57). If a potential safety concern is identified related to exposure to the excipient, alternatives should always be considered. Another dosage form or even a different route of administration might be necessary to avoid significant risk. Further non-clinical safety evaluation and specific clinical monitoring in paediatric studies might be needed. Combinations of excipients sharing the same metabolic pathway may increase the risk of accumulation of excipient. 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 proven.

If excipients of potential concern are included, information should be provided on the package or in product information related to the potential risks to the patients.

Falsified (58, 59) starting materials, including substituted raw materials, may result in serious injury or death, particularly in children. Manufacturers of medicines should ensure that raw materials are acquired from qualified and approved suppliers. In particular, for high-risk excipients that may be

contaminated with highly potent substances, for example, diethylene glycol or ethylene glycol contamination in propylene glycol, glycerin or sorbitol, manufacturers are alerted to take control measures to ensure the safety, purity and quality of such excipients and FPPs (*59*–*61*).

4.3.1 Specific groups of excipients

The list below is not exhaustive, but provides examples of excipients with specific considerations for paediatric formulations.

Colouring agents

Colouring agents can serve different purposes, including identification, light protection and flavour matching. The use of colouring agents in paediatric medicines is generally discouraged, in particular in medicines for infants and young children, and natural colourants should be considered if possible. Their use may, however, be justified in certain cases, for example, to avoid accidental dosing errors in connection with medicines produced in several strengths. In this case, solid dosage forms, such as tablets and capsules, may be preferred, because size, shape, printing and embossing can facilitate the identification of different strengths of the preparation.

Some colouring agents used in paediatric medicines have been associated with hypersensitivity and allergic reactions. For some colouring agents, such as azo dyes, there are controversial views on their use in children, and alternatives are recommended.

Preservatives

Medicinal products may require antimicrobial preservatives to avoid microbial proliferation during storage, in particular under in-use conditions. Preservatives are needed, especially for aqueous multidose preparations and semi-solid preparations, and may also be needed for other aqueous preparations.

Preservatives may have a potential to cause adverse reactions, in particular in infants and neonates, and they should be avoided in paediatric formulations wherever possible. However, the use of preservatives may be required for multidose dosage forms. The use of new preservative systems shall be justified and supported with data on its safety profile. Sterile products and large-volume parenterals intended for single use, and ophthalmic preparations intended for neonatal use, should not contain preservatives, and alternative preservation strategies, such as single-dose units, should be considered. When preservatives are required, their concentration should be of the minimum level consistent with satisfactory antimicrobial function in each individual preparation, and a thorough justification of the choice of the preservative should be established. Mercury-containing preservatives (for example, thiomersal) should be avoided.

Parabens are used in food and cosmetics and are the most commonly used preservative in pharmaceutical products. In vitro and animal toxicity reports have associated some parabens (for example, propylparaben, but not methylparaben) with reduced spermatogenesis and oestrogenic activity. The European Commission Scientific Committee on Food recommends an acceptable daily intake of up to 10 mg/kg/day as the sum of methyl, ethyl and propyl paraben and their sodium salts. A permitted daily exposure value of 2 mg/kg/day is recommended for the use of propylparaben in adults and paediatric patients. The use of methylparaben in oral formulations up to 0.2% (as within the recommended effective concentrations as a preservative) was not considered a concern for humans, including the paediatric population, whatever the age group (*49*, *51*).

Sodium benzoate is another commonly used preservative in oral liquid products. Safety concerns exist in neonates, specifically jaundice and metabolic acidosis, and it is therefore not recommended in this age group. The acceptable daily intake for adults and children above 4 weeks of age is 5 mg/kg/day (*52*).

For benzyl alcohol, there is a risk of accumulation in newborn babies, and its use has been linked to "gasping syndrome" when given intravenously at high doses (100–200mg/kg/day) to preterm newborns. Despite limited data on the actual safety threshold, it is not recommended for use in neonates, and should be used with caution for long-term use in children aged below 3 years.

Taste masking and sweetening agents

Taste masking in medicines for oral use is often needed to improve the palatability of the medicine. Children have a well developed sensory system for detecting tastes, smells and chemical irritants (*62*). They can 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 (*63*, *64*). Often, children seem to prefer sweeter tastes than adults do. The unpleasant taste of an API, for example, a bitter or metallic taste, is therefore often masked by the use of sweetening agents and flavours. However, the rationale for the use of a particular sweetening agent in a paediatric preparation should be clearly described and justified taking into account current practice on sensory analysis. The latest guidance on sensory analysis has been published by the European Paediatric Formulation Initiative (*64*). Other taste-masking methodologies should be considered, including their potential impact on mouthfeel and pharmacokinetics.

It is important to ensure the safety of the sweetening agent in relation to specific conditions of the child (for example, diabetes, fructose intolerance or patients on a ketogenic diet) and possible side-effects. Attention should be paid to the following.

- Sorbitol is a monosaccharide and, when ingested orally in large amounts, it can cause a laxative effect and gastrointestinal discomfort. The European Medicines Agency recommends a maximum dose of 140 mg/kg/day for children and adults (*65*). Other poorly absorbed sweeteners, such as mannitol and xylitol, may also cause the same effects as sorbitol.
- The use of aspartame in patients with phenylketonuria should be avoided, since it is a source of phenylalanine. Furthermore, aspartame should be avoided in infants aged less than 12 weeks; the United States Food and Drug Administration and European Medicines Agency have recommended a maximum dose of 40 mg/kg/day (*66*).
- Some sweeteners can cause dental caries.

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

Paediatric preparations should not become too enticing to children, as this is known to increase the rate of accidental poisoning.

An example of a qualitative evaluation of taste by a taste panel for zinc formulations can be found in the United Nations Children's Fund/WHO publication on production of zinc formulations (*67*, *68*).

Another example is a primaquine formulation where development was assisted by sensory evaluation methodologies to optimize formulation design (*69*).

Solubility enhancers

The aqueous solubility of the API may limit the concentration achievable in formulated solutions and, hence, the desirable dose volume. Often an acceptable solution requires the use of solubility-enhancing excipients, for example, non-ionic surfactants and co-solvents such as glycerol, liquid macrogols, polysorbates or 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 to intestinal tissues in neonates caused by hyperosmolality or other local toxicity. Risks associated with the use of solubility enhancers may be higher when they are included in parenteral preparations due to their exposure profile.

Ethanol should not be included in medicines for children unless it is absolutely necessary. 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. It is also recommended that manufacturers of existing formulations containing ethanol should consider reformulation if the medicine is intended for paediatric use.

Children do not metabolize ethanol as efficiently as adults due to immaturity of metabolic enzyme activity. Alcohol dehydrogenase is the main enzyme responsible for metabolism of alcohol, and it does not reach adult activity until 5 years of age (*70*). Furthermore, ethanol presents a risk of drug interactions, for example with drugs that may amplify central nervous system depression, including anxiolytics, antihistamines, hypnotics and opioids. Also, it can lead to pharmacodynamic interactions manifesting as sedation, tachycardia and a heightened risk of intoxication (*71*). Furthermore, polypharmacy can lead to high levels of exposure among neonates in intensive care settings, where multiple medications containing ethanol as an excipient may be administered concurrently (*72*, *73*).

Exposure to ethanol is often limited when used as an excipient in medicines; however, it is important to note that the effect on the health and development of children of long-term exposure to even low levels of ethanol in medicines still requires full evaluation, as it is already known that toxic effects on liver function and brain maturation in young children are likely, as supported by non-clinical or limited clinical data and case reports.

Reflections on the safety of ethanol, including for children, and the thresholds for warning statements in the package information have been given by regulatory authorities (*49*, *50*, *74*). For example, the European Medicines Agency recommends that package leaflets include specific warnings regarding oral ethanol exposure in children (*50*). Ethanol levels of 15 mg/kg may cause drowsiness in younger children, while doses of 75 mg/kg are likely to affect behaviour, impair concentration and induce sleepiness. The European Medicines Agency recommends that blood ethanol levels do not exceed 1 milligram per decilitre (mg/dL) after a single dose (or a dose of 6 mg/kg) in children younger than age 6 years and 12.5 mg/dL (or a dose of 75 mg/kg) in patients aged 6 years and over (*49*, *50*). The United States Food and Drug Administration sets a maximum limit of ethanol as an inactive ingredient in oral over-the-counter products of up to 0.5% for children aged under 6 years; 5% for children aged 6 to 12 years; and 10% for anyone aged 12 years and over (*74*).

Propylene glycol is another co-solvent used in liquid preparations. Similarly to ethanol, it is metabolized by alcohol dehydrogenase. Metabolic and neurological adverse effects have been reported with high amounts of propylene glycol used in paediatrics. The European Medicines Agency has given the following advice on safety limits for maximum daily amounts of propylene glycol: up to 1 mg/kg for neonates; 50 mg/kg for age 1 month up to 4 years; and

500 mg/kg for 5 years of age and above, including adults, mainly based on limited safety data (*53*).

Note: see Appendix 2, *List of examples of high-risk excipients and contaminants*, of the *WHO good manufacturing practices for excipients used in pharmaceutical products* (*75*).

4.4 Packaging and labelling

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

- permit accurate dosing and convenient administration;
- prevent accidental consumption, for example by using childproof caps in oral liquid medicines or blister packs that cannot accidentally open easily;
- protect the integrity of the product;
- are robust and convenient for the supply chain (that is, transportable);
- are tailored to the target age group;
- contribute to in-use stability;
- provide appropriate information on the use of the medicine with unambiguous labelling of dose strengths, concentrations and clear method of administration. Ideally, this information must be assessed by parents and caregivers according to age groups. Unclear labelling can risk accidental administration by caregivers.

In cases where the formulation or dosage of a paediatric medicine is significantly different from a similar adult medicine or paediatric medicine, it is important to have noticeably different product packaging for the two products to avoid administration errors. It is necessary that consideration be given as to whether the medicine is to be packed in a child-resistant container, using packaging that is difficult for young children to open but not unduly difficult for adults to open properly. Making medicines similar to candies or sweets in the hope of improving compliance should be avoided, since it could lead to an accidental overdose.

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

- the medicine is easy to use;

- pharmaceutical forms are easily ingested, such as drinkable forms or orodispersible tablets;
- separation of the day dose pack is facilitated (that is, it can be easily carried by the patient in their 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 (for example, as milligrams per kilogram of body weight). Specific instructions about how to measure and administer a precise dose should be provided.

Drawings or pictograms showing the time, method and route of administration are strongly recommended (perhaps aided by the use of QR codes instead of printing). They should be subject to readability and comprehensibility tests by target groups or caregivers.

5. Routes of administration

The routes of administration and formulations listed in this section are not exhaustive, but information is provided for cases where specific considerations for the paediatric population are required.

5.1 Oral and enteral administration

The oral route is the preferred and most commonly used route of administration for neonatal and paediatric patients. This route is generally acceptable in all age groups if the medicine is administered in a suitable dosage form. Strictly speaking, the choice of dosage form for oral or enteral administration depends on both age and clinical condition.

During paediatric formulation development, consideration should be given to the effects of increased gastric pH and intestinal motility at birth and in early infancy (*9*), as well as the limited and variable gastric and small intestinal fluid volumes in paediatrics. Mean fasted gastric volume in paediatrics (age range of 2 months to 18 years) has been reported to be 0.35 ± 0.45 mL/kg with a range of 0 to 3.14 mL/kg, while small intestinal fluid volumes have been reported to be 0–51 mL in the fasted and 6–91 mL in the fluid-fed state (*45*, *76*). In addition, the gastric emptying of sick newborns is most erratic and can be delayed. Further information can be found in a European Medicines Agency guideline on medicines for term and preterm neonates (*15*).

For oral solid medicines that require precise dose measurement or titration, suitable dosage forms could be based on a platform technology to produce multiparticulate solids, for example, minitablets or spherical granules (pellets), that allow production of dosage forms of varying strength, as well as different

dosage forms such as 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.

It is preferable that the dosage form is acceptable and palatable in itself without any need for further modification. The caregiver may, however, attempt to improve the ease of administration and acceptance of the medicine by mixing with food or a beverage (*77*). 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 or formula milk) is foreseen, this eventuality should be evaluated by the appropriate compatibility studies (*41*, *77*). Information should be provided in the patient information leaflet by the manufacturer, as supported by evidence-based studies. Regional and cultural differences regarding preferred tastes and practices may need to be considered.

The European Paediatric Formulation Initiative has recently published *A guide to best practice in sensory analysis of pharmaceutical formulations* to facilitate the understanding and optimization of the sensory characteristics (such as, taste, flavour or mouthfeel) of the formulation throughout the development of the pharmaceutical product to enhance palatability and acceptability (*64*).

5.1.1 Administration through enteral feeding tubes

For neonates, seriously ill infants and children, as well as for certain medical conditions, enteral administration of medicines via enteral feeding tubes is used, requiring some specific considerations. Therefore, data supporting such administration should be provided if targeting such patient populations. These considerations should be highlighted in the product information.

In order to evaluate potential bioavailability changes, the site of absorption of the API needs considering, as well as physicochemical properties of the formulation, such as pH (drug and site of absorption), viscosity, particle size and any potential risk of adsorption of the API to the tube material. These are all important factors for dose recovery at the end of the tube and will have an effect on rate and extent of absorption. The width and length of enteral feeding tubes used across different ages will need careful consideration; for instance, viscous drugs may lead to blockages of very narrow tubes, such as the ones used in the neonatal population (3–8 French size). If dosage forms require manipulation for administration by enteral feeding tube, the information will need to be provided as part of the product information once all assessments are conducted, as mentioned above. Furthermore, testing of multiple administrations through one tube should be considered, if a drug product will be administered multiple times in a 24-hour period (*77*).

The flushing volume should be appropriate to the target age group and an acceptable fluid intake.

Further information is provided in guidance from the United States Food and Drug Administration and European Medicines Agency (*78*, *79*).

5.1.2 Pharmaceutical forms

A. 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 disintegration in the mouth (chewable tablets, orally dissolving tablets or orodispersible tablets). Some are intended for swallowing after dissolution or dispersion in water or other suitable liquid. Their advantages over oral liquid preparations are improved physical and chemical stability, good dosage uniformity, lower amounts of potentially harmful excipients, and easier storage conditions and transport. The acceptability of oral solid dosage forms highly depends on the product attributes, product and patient interface and child characteristics.

Flexible solid dosage forms, in general, are likely to prove most suitable for global use, including for developing countries, and should be prioritized. These include tablets that are orodispersible or can be used for preparation of oral liquids suitable also for the younger age groups (for example, dispersible and soluble tablets). The flexible dosage form design may be used for various APIs. Provided that the medicine can be dispersed in milk, it could potentially be used in very young children (aged under 6 months). It is necessary to identify appropriate product strengths and ratios of active ingredients for each medicine and to ensure that package sizes will allow optimal use under public health programmatic conditions.

Capsules

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

Capsules are often intended to be taken as whole. Acceptability highly depends on the size of the capsule and the age of the child. The smallest possible size should be encouraged. Alternative strategies for administering capsules should be envisaged by developers and manufacturers. For example, hard capsules may be opened and their contents taken as such, or taken after mixing with food or sprinkling onto food, but this is not always appropriate (for example, due to taste issues, exposure risks or impact on bioavailability). For capsules with enteric coated pellets or prolonged release granules, dispersion in fluid may be required, avoiding crushing.

Instructions on the proper use of a capsule formulation must be provided on the label to facilitate correct administration.

Immediate-release tablets

Conventional tablets are either uncoated or 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 and swallowability.

Acceptability of tablets depends on the size of the tablet and the age of the child, their condition, and if they can swallow tablets. Traditionally, adult-size capsules and tablets have not been considered appropriate for younger children, and alternative dosage forms have often been requested below the age of 6 years. The increased availability of smaller tablets (including minitablets) has emphasized the need for more flexible and scientifically based considerations, as more data emerge on acceptability related to tablet size and patient age. Several studies have indicated that children, infants and neonates could be able to swallow tablets provided size is sufficiently small. For example, neonates may be able to swallow a 2-millimetre (mm) tablet (*80*), and small oblong tablets (2.5 x 6 mm) may be well accepted in infants and toddlers (*81*). More data for international guidance regarding acceptability of oral dosage forms and their potential risks (for example, choking or chewing) in small children, as well as in older children and adolescents (for example, their acceptance of large tablets or capsules), are still needed.

Therefore, the smallest possible tablet size should be encouraged, and the appropriateness of the tablet size should be confirmed during product development.

Alternative design strategies to facilitate proper dosage administration should be considered by the manufacturer, for example, score lines to facilitate breaking and simplify swallowing, as this will increase administration flexibility and therefore adherence.

Functional score lines 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. Multiple score lines may create risk of dosing errors and should be justified. Information on testing requirements for tablet scoring can be found in regulatory guidance documents, such as those of the United States Food and Drug Administration (*82*) or *The International Pharmacopoeia* (*38*). Score lines intended to ease administration (and not to provide, for example, half dose) should be clearly identified in the product labelling. It is preferable that the single part of the broken tablet contains the amount of API suited to the youngest intended age group.

Caregivers often crush tablets to increase adherence. Crushing may, however, result in dosing inaccuracies, affect the bioavailability of some medicines, and disclose poor-tasting, toxic or irritant APIs. The effect of crushing tablets

should be investigated by the manufacturer, in particular when swallowability challenges may be a concern, and this information should be provided in the patient information leaflet.

Powders and multiparticulate preparations

Powders and multiparticulates are provided in sachets, hard capsules or in blister packs that allow the contents to be taken directly or after manipulation – for example, preparations mixed with water or milk could be acceptable from birth, depending on dispersing or dissolving characteristics, taste and compatibility. When stated to be mixed with food, such products may be acceptable from the moment the infant is able to accept solid food (about age 6 months).

Multiparticulate preparations are granules, spherical granules of uniform size (often called pellets) and minitablets. Pellets are often prepared by extrusion or spheronization technology, which produces uniform particles within the size range 0.5–2 mm. Minitablets are prepared by compression into units typically with a diameter of not more than 3–4 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 youngest target age group.

These preparations offer the same advantages as conventional tablets and capsules with regard to the use of excipients, opportunities for taste masking (for example, by coating), stability, and opportunities for modifying the release profile. Furthermore, they possess great dosing flexibility. An age-appropriate dosing may be achieved by adjusting the number of pellets or minitablets. A counting or measuring device may be necessary when a large number of pellets or minitablets is required; however, this is still an area requiring further development, due to its technical complexities.

Chewable tablets

Chewable tablets are intended to be chewed and swallowed. They should possess good organoleptic properties, including a good texture and mouthfeel, which is influenced by the solubility of the API, particle size and shape of the formulation, 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. 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 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 labelled with clear instructions covering all the administration options.

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.

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 should not be ingested 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 some clinical conditions, such as renal insufficiency.

Dispersible and soluble tablets

Dispersible and soluble tablets are oral solid dosage forms intended to be dissolved or dispersed in water prior to administration, and may have a significantly better acceptability profile than effervescent dosage forms. Problems mentioned above for effervescent dosage forms 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. Container rinsing may be needed. 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.

Orodispersible dosage forms

Orodispersible dosage forms are orodispersible tablets, oral lyophilisates and thin films to be placed in the mouth where they disperse rapidly into small-sized particles or "melt" by dissolution in the saliva, after which the dose is swallowed.

These forms are attractive as they may be acceptable to the same age groups as liquid preparations without the need for a liquid vehicle for administration. In some situations, especially with younger children, it may still be useful to disperse in a small volume of liquid prior to administration to improve acceptability.

Orodispersible tablets designed to disintegrate rapidly are prepared by compression of a formulation containing, for example, mannitol, a superdisintegrant and a flavouring agent. The amount of API that can be

incorporated is limited. Therefore, only high-potency APIs are suitable for the wafer or flat film development. Orodispersible tablets are flexible dosage forms particularly well suited for highly water-soluble APIs. However, they are not suitable for drugs that cause irritation. The product may be moisture sensitive, requiring special packaging, and may offer a shorter expiration date (66).

More recently, 3D printing has been utilized to produce orodispersible tablets. Different types of 3D printing can successfully produce oral solid dosage forms, with binder jetting (drop-on-powder printing) and fused deposition (melt extrusion) the most explored. As of 2015, levetiracetam orodispersible tablets, produced by binder jetting, have been approved by the United States Food and Drug Administration. They are highly porous tablets that rapidly disintegrate with a sip of water and are available in dose strengths of 250, 500, 750 and 1000 mg indicated for epilepsy in patients aged 4 years and older and weighing more than 20 kg. Orodispersible tablets thus enable the administration of high dose strengths to children.

Oral lyophilisates are prepared by the 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. 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.

Orally dissolving films present rapid disintegration and dissolution qualities. They are easy to administer in children and useful in cases where rapid action is required, such as motion sickness, allergic reactions, cough, bronchitis, asthma and pain.

Orodispersible dosage forms are mainly 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.

Sustained-release formulations, solid

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, for example, as multiparticulate solids provided with a barrier coating, in sachets, as 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 that may improve adherence. 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 (*83*).

In the development of sustained-release formulations (solid or liquid) for paediatric use, special attention must be given to the physiological conditions of the child to be treated and their variability, for example, gastric pH and emptying rate and intestinal motility.

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 be included on the label.

B. Oral liquid formulations

Oral liquid preparations include aqueous solutions, suspensions, emulsions and syrups. They are the most used and often most convenient preparations for children in the youngest age groups or patients with conditions hampering the ability 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 (for example, antimicrobial preservatives or solvents) and taste masking 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. What is considered an appropriate volume will depend on several factors. Typical target dose volumes are 5 mL or less for children aged under 5 years and 10 mL or less for children of 5 years and older; however, the more palatable the formulation, the higher the dose volume that will be accepted by the child.

Oral liquid preparations may be supplied in multidose containers or single-dose containers. Usually, both forms require antimicrobial preservatives when presented as ready-to-use liquids. Special attention must be paid to the in-use stability of multidose preparations, both microbial and physicochemical.

Multidose preparations must be packaged together with an appropriate dosing device. The correct graduation of the device with the expression of dose in mass (mg for example) (not in volume, as this requires conversion and thus

risks calculation errors) and its accuracy must be evaluated by the manufacturer. Generally, oral graduated syringes are preferable because of the flexibility in dose measurement and superior accuracy compared to other devices, such as graduated pipettes (plastic spoons should be avoided whenever possible). However, special consideration should be given when small volumes, less than 1 mL, are required, since the accuracy of oral syringes can be variable depending on the dose volume size; in particular, the variability increases if volumes are below 0.25 mL (*84*). Information about the requirements of oral syringe graduation and the measuring of small volumes is described in the European Medicines Agency question and answer document (*85*).

The risks associated with incorrect dosing should be considered. If correct dosing is critical, the administration device required should be provided as part of the medicine packaging and properly tested by the manufacturer for accuracy. Prefilled oral syringes could also be considered, although more costly and with potentially less flexibility in dosing.

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 minimized by selecting appropriate suspending agents and taste-masking excipients.

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 risk of unreliable dosing is higher with suspensions compared to solutions, as carers may forget to shake the formulation or allow a prolonged time interval between shaking and administration, which may lead to sedimentation of the formulation.

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). The solids must be easily dispersed or dissolved within a short time once the vehicle is added. Powders and granules for reconstitution are produced as single-dose sachets or multidose preparations, usually provided in bottles or containers that can hold the reconstituted multidose preparation. The liquid vehicle can be provided together with the dry preparation. Manufacturers should provide clear instructions on how to reconstitute and administer the product in the product information, for example, with boiled or cooled water.

Drops

Some liquid medicines are administered as drops in small volumes using droppers or a graduated pipette to administer the dose directly to the patient, or 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, taking into account the potency of the drug, side-effect profile and risk of dosing errors (for example, risk of confusion in calculating the number of drops required for a given dose, or risk of carers miscounting the drops at the time of administration). Special caution should be taken for very young children and for APIs with a narrow therapeutic index, in which cases this form would generally not be recommended. The in-use performance of the dropper is critical for this dosage form. It is recommended that carers are clearly instructed to hold the dropper in a vertical position to ensure uniformity of drop size (*86*, *87*).

Clear instructions as part of the product information and packaging are necessary.

Modified-release liquids

Oral liquid sustained-release (or prolonged-release) formulation may be manufactured using specialized technologies, such as suspensions of coated multiparticulate systems, (coated) ion exchange resin complexes with diffusion-controlled release, or in situ gelling systems that modulate gastric residence and diffusion.

For gastro-resistant products, suspensions of coated multiparticulate systems could be applicable, but generally these products are manufactured as solid formulations that may be dispersible in a liquid or vehicle.

Key development considerations include ensuring uniform redispersibility of the suspension, minimal viscosity changes over shelf-life and in use, and robust release control after dispersion or coadministration with common vehicles (water, milk or fruit puree).

For gastro-resistant products, the pH of the liquid (for dispersion) or vehicle is critical, as these products are designed to withstand acidic conditions.

5.2 Rectal administration

Rectal administration is an important route that can be used for both local effects (for example, laxative and anti-inflammatory) and systemic effects (for example, antipyretic and anticonvulsive) in all age groups. This route of administration is especially valuable when the oral administration is not feasible due to the condition of the child or palatability issues with an oral formulation. It can also be used as an alternative to parenteral preparations for severely ill children and for indications such as severe malaria, pain, infection and nausea or vomiting. There may, however, be cultural barriers to the use of rectal preparations.

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 content 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, for example, 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. Information on how to prevent the above and what action to take by health care givers if it occurs needs to be provided in the product information by the manufacturer.

Adherence for rectal preparations may be lower than for oral dosage forms, depending on age, condition and cultural factors.

Suppositories

The design, and particularly the size, of suppositories for use in paediatric patients must be tailored to the age or size of the child. The 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 that can be cut into smaller portions, ensuring delivery of an appropriate dose. In this case, the manufacturers should provide clear instructions on how to cut them in the product information, and the acceptability of cutting should be studied as part of the product development.

Two types of suppository base are available: a base insoluble in water (for example, hard fat), which melts below body temperature; and a base soluble in or miscible with water (for example, macrogols), which dissolves in or mixes with the rectal liquid vehicle. Both types may be irritants and with suppository melt formulations, special consideration must be given to storage temperature.

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 and 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 rectum size of the child and should not cause injury. The use of prefilled 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. Acceptability of rectal preparations needs to be part of the product development.

5.3 Parenteral administration

Parenteral administration refers to the administration of medicines via the intravenous, intramuscular or subcutaneous route.

Commonly, these routes of administration require the parenteral drug to be administered using a syringe or needle. Most children have a fear of injection needles and, in some circumstances (depending on drug, condition or other factors), there are possible alternatives that prevent multiple injections, for example, a depot injection in the case of long treatment duration. Also, needle-free injection devices (jet injectors) that drive small droplets through the skin by high pressure could be considered for subcutaneous administration (for example, in the case of growth hormone treatment or local anaesthesia prior to a procedure). However, experience of their use in paediatric populations, especially in smaller children, is limited.

When the intravenous route is required, catheters and injection ports that can remain in place for the length of the treatment can also prevent the need for repeated injections. Devices that offer comfort and fit into daily activities can alleviate patient distress and encourage adherence. Moreover, incorporating features that simplify maintenance and enhance infection control can significantly lessen the burden on patients and health care providers alike.

Occasionally, long-acting injections can be administered intramuscularly or subcutaneously to help reduce the number of injections, but this approach requires consideration of blood perfusion patterns in different childhood ages as well as benefit–risk balance, since the management of potential side-effects would be difficult if they occur (*88*).

5.3.1 General parenteral formulation design aspects

Aqueous preparations (solutions or suspensions) must be adapted to the physiological conditions of the administration site. The tolerances for deviations in pH and osmolality are dependent on the route of administration. Hyperosmolar or extreme pH injections may cause pain and irritate peripheral veins. Information on pH and osmolarity should be specified in the product information.

Co-solvent formulations may be administered parenterally; however, rate of administration is critical, as there is a risk of drug precipitation upon exposure of the drug formulation to aqueous blood.

Attention should be paid to the potential adsorption of the API onto the surfaces of plastic containers, intravenous bags, tubing, catheters and other administration equipment. This is important, for example in the case of neonatal care, where doses are small and any significant adsorption may decrease the amount of drug that the patient receives (such as insulin). Compatibility studies should be performed on packaging and delivery components to ensure that there is no adsorption. Attention should also be paid to leaching of plasticizers from the materials to the parenteral preparation (*89*).

Some APIs are presented as powders or lyophilisates to be reconstituted before administration. It is important that clear instructions on the reconstitution, including displacement values, and further dilution requirements (such as volumes or diluents) are clearly described in the product information. Information on the size of syringe that permits accurate administration would also be helpful.

Information on storage conditions and stability of product after reconstitution and during the length of administration needs to be provided in the product information.

In the case of intravenous or subcutaneous administration, if the medicinal product is likely to be coadministered using the same line as other treatments, compatibility with concurrent medication should be studied (for example, other intravenous medication through the same line, including total parenteral nutrition, or even mixed in the same syringe, as is the case in drugs administered via the subcutaneous route in palliative care) (*90*).

Specifications of syringes and giving sets used in clinical trials should reflect as closely as possible normal clinical practice (for example, tubing of representative length and diameter, the dead space volume of the administration set, and needle and syringe sizes). Detailed information on devices should be documented in the product information where appropriate.

5.3.2 Intravenous route

The intravenous route is preferred for seriously ill children, for clinically unstable term and preterm neonates, and in some specific conditions.

Age- and weight-related preparations, considering formulation concentration and required injection volume, are preferred in order to provide an acceptable dose volume. This approach prevents dosing errors associated with the use of multidose preparations (or vials designed for adults containing many doses for a small child) that will require calculation of the dilution needed to obtain measurable volumes.

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. In general, the volume in the vial should be no greater than 10 times the smallest dose to be measured.

Formulations for neonatal patients are usually aqueous solutions intended for intravenous administration. Fluid volumes and electrolyte contents are important for all paediatric patients; however, these are critical for neonates (*91*).

Specific points to consider for administration of intravenous parenteral preparations

Often the intravenous drugs are administered as infusions via catheters. In neonatal care, it is important to consider the potential lag time between the infusion and delivery of the medicinal product to the blood circulation. Administration of the complete dose must be ensured.

Safety measures and clear information on administration via central or peripheral access should be provided, including advice on maximum and minimum dilutions for safe administration.

Consideration should be given to the child's fluid and electrolyte balance contribution of the diluted product, and addition to the volume and electrolyte content of the formulation prior to dilution, which is especially important in neonates as it can provide a significant amount of their daily allowance. Caution needs to be taken in the case of premature neonates with immature renal function and patients with renal failure when using sodium chloride as a diluent, as plasma sodium can rise and needs to be monitored accordingly.

Complex calculations and processes involving several dilution steps to obtain a final product for administration (for example, dose in micrograms/kg/hour prescribed to be converted to volume per hour administered; conversion between millimole (mmol) prescribed and mg on the label; conversion between mg prescribed and percentage concentration on the label; and decimal points) should be minimized to prevent errors in preparation and administration of intravenous drugs and prevent the risk of microbial contamination. The measurement of volumes smaller than 0.1 mL should not be required, as this is not possible to measure accurately in clinical practice with the syringes available.

Intravenous continuous infusions used in paediatric care have traditionally been prepared individually at the bedside in many countries, by adding a weight-based amount of the medicine to a fixed volume of diluent (typically 50 mL). This individualized, patient-specific approach provides a consistent relationship between the infusion rate and the delivered dose across different patient weights. For example, adding 0.3 mg/kg of adrenaline to 50 mL of sodium chloride 0.9% or glucose 5%, run at 1 mL/hour, provides a dose of 0.1 micrograms/kg/minute, irrespective of patient weight. However, this practice is associated with

preparation errors, including significant variability in concentrations, particularly when small volumes are involved (92–96).

An alternative is to use a standard concentration (StdC) infusion, where the drug concentration is the same across a range of patient weights (for example, 100 mg of drug in 50 ml diluent). This approach loses the interpretable, volume rate to drug dose relationship described above, and means that StdC infusions typically require the use of medical infusion devices or "smart pumps" pre-programmed with a drug library that provides information such as defined concentration and dosing limits to assist with dose and volume (infusion rate) calculations. The StdC approach has been increasingly adopted to prevent medication errors in neonatal and paediatric care (97–99). Several national and profession bodies across different regions have recognized or promoted this approach as part of good practices, for example, organizations responsible for health care accreditation, medicine regulation, medication safety and paediatric clinical standards in various countries (100–103). This experience demonstrates how the StdC approach can support product developers in designing ready-to-administer products to improve safety and usability.

Although the use of infusion pumps is the recommended safest option for delivery of some critical therapies for critically ill neonates and children, in some low-income countries these devices are not available or there are technical difficulties related to their use, such as lack of electricity supply or technical support (104–106). The provision of dosing tables for calculating the volume (in mL) (dose/kg/hour converted to mL/hour) or drops required for a given dose and weight to be administered via either a pump or gravity giving sets can provide significant support to health care staff and prevent errors. The use of gravity giving sets and the practice of visual calculation of drops carries its own risks and ideally should not be used. However, if there is no choice, there need to be strict procedures in the clinical setting and emphasis on education and training.

Detailed information on the process of intravenous administration should be included in the product information, clearly stating the dose, volume to be measured and steps required, and how this can be achieved safely and accurately.

Intramuscular or subcutaneous routes

Some parenteral preparations are administered by the subcutaneous or intramuscular route, for example, vaccines. The intramuscular route of administration is usually not indicated for neonates because of unpredictable or slow absorption, physiological reaction to injection pain and potential for tissue damage. The limited muscle mass of newborns and, in particular, of preterm infants constrains the use of intramuscular injections, although there are exceptions, for example the administration of vitamin K or vaccines. Other routes of administration, for example intraosseous, are used in emergency cases.

A pH close to the physiological one is recommended to minimize pain for subcutaneous administration. Subcutaneous administration is highly sensitive because the release of the volume from the injection site proceeds slowly and can cause irritation and tissue damage.

Particular attention should be given to the subcutaneous bolus injection volume. The volume of injections must be kept to the minimum possible to reduce pain. Reported outcomes from older children and adults suggest that volumes of up to 0.5–0.8 mL do not increase substantially the pain associated with administration beyond that produced by the needle insertion. In neonates, however, there is an absence of data; hence, injection volumes should be kept lower than above where possible or otherwise appropriately justified (*107*). To minimize pain, a needle gauge size of 26–30 and low volumes (≤ 0.5 mL) are recommended, and accuracy of intended devices (syringes and needles) needs to be justified (*108*).

Drugs can also be administered via subcutaneous infusion where larger volumes can be administered over time, for example in palliative care. Some considerations on infusion compatibilities and catheters used were already discussed in subsection 5.3.2.

5.4 Dermal, transdermal and intranasal administration

5.4.1 Dermal

Preparations for dermal (or cutaneous) administration include liquid preparations (lotions and shampoos), semi-solid preparations (ointments and creams), solid preparations (powders) and patches. 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 and this is not a recommended route of administration in this population, given the unreliable absorption and potential for toxicity. Children have a lower volume of distribution per unit area of skin.

Depending on the dosage form, different excipients are needed. The safety profile of each must be considered, 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.

In the case of patches for dermal delivery, the size, shape, cutting and adhesive outlined in the following subsection should also be assessed.

5.4.2 Transdermal

Transdermal patches are used for systemic delivery of APIs that 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 that 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 (following all the required testing), information on the cutting technique should be provided as part of the product information 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.

Microneedle technology is being studied as a strategy to surpass the stratum corneum barrier in a minimally invasive manner that does not affect the nerve endings or blood vessels, and enables the successful passage of drugs (at smaller doses required in children) by creating transient channels across the skin (*109*).

5.4.3 Intranasal

Nasal drug delivery offers a convenient dose presentation that could be highly suited to local, systemic or direct nose-to-brain drug delivery in certain paediatric drug delivery settings. Nasal sprays of antihistamines and steroids for treating seasonal allergic or non-allergic rhinitis allow fast relief of symptoms and reduced side-effects compared to the oral route.

Systemic delivery via the nasal route bypasses first-pass metabolism, and in brain delivery via the nasal route there is direct drug transport via olfactory and trigeminal pathways to the brain, bypassing the blood–brain barrier, in both cases enabling a rapid onset of action. Several pharmacotherapeutic agents are administered nasally for systemic effects, for example, glucagon for severe hypoglycaemia in diabetic patients, desmopressin for diabetes insipidus or primary nocturnal enuresis, diazepam for episodes of frequent seizure activity, or analgesic agents such as diamorphine for severe procedural pain relief, for example in the case of fractures. Intranasal vaccines can achieve a local or systemic antibody response and provide rapid mass immunization without the need for a sterile product.

The nose-to-brain direct route is a very novel route under investigation at early development stages for treatments such as gene therapy or oxytocin, and it may find its clinical use for the management of some paediatric conditions in the future (*110*, *111*).

5.5 Inhalation route

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 physiology of children of different ages and their ability to use the devices correctly should be considered in the development of paediatric inhalations (*112*). 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 transferring 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 (*113*). 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 or 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, though it is bulky and presents disadvantages if it needs to be carried around. For children aged younger than 2–3 years, a face mask 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 aged 4–5 years, as minimum inspiratory flow is required. DPIs and MDIs are preferred for older children because of their portability and convenience.

5.6 Intrathecal and intracerebroventricular routes

The therapy of central nervous system disorders is complex, as many drugs do not cross the blood–brain barrier. A wide variety of antibiotic, antineoplastic, analgesic and antispastic drugs have been administered directly into the cerebrospinal fluid. Analgesic and antispastic drugs are administered intrathecally into the cerebrospinal fluid surrounding the spinal cord. The intracerebroventricular route is preferred for antibiotics and antineoplastic drugs because administration via this route ensures a more homogeneous drug distribution throughout the cerebrospinal fluid space, via Ommaya reservoirs for repeated access or catheter

insertions for single use. The drug concentration is very important to prevent complications, for example, arachnoiditis with some chemotherapy. Moreover, the pH of solutions and buffering excipients needs to be carefully selected for isotonicity, as well as the flushing techniques (*114*–*116*).

New evidence is emerging in this field as even some gene therapy administration is proposed via these routes (*117*).

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