World Health Organization

DRAFT WORKING DOCUMENT FOR COMMENTS:

Development of paediatric medicines: points to consider in formulation

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For any technical questions, you may contact **Dr Steve Estevão Cordeiro**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (estevaos@who.int), with a copy to **Ms Sinéad Jones** (jonessi@who.int).
Comments should be submitted through the online platform on or by **7 March 2025**. Please note that only comments received by this deadline will be considered for the preparation of this document.
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SCHEDULE FOR DRAFT WORKING DOCUMENT QAS/24.950:

Development of paediatric medicines: points to consider in formulation

Description of activity	Date
Preparation of first draft working document by lead expert.	May 2024
Virtual meetings from drafting group to review initial draft.	June - November 2024
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	January - March 2025
Consolidation of comments received and review of feedback. Preparation of working document for discussion.	March - April 2025
Drafting group meeting (if applicable).	April 2025
Discussion of the feedback received on the working document in a meeting with an informal consultation group.	May -June 2025
Drafting group meeting (if applicable).	July 2025
Mailing of working document to the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations (EAP) inviting comments and posting of the working document on the WHO website for public consultation.	July – August 2025
Consolidation of comments received and review of feedback. Preparation of working document for discussion (if applicable).	August - September 2025
Drafting group meeting (if applicable).	September 2025
Preparation of a working document for discussion and possible adoption by the ECSPP.	September 2025
Presentation to the fifty-ninth meeting of the ECSPP.	October 2025
Any other follow-up action as required.	

Development of paediatric medicines: points to consider in formulation

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1. Introduction

This guideline aims to highlight areas of specific attention when developing medicines for children, however, 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 age-appropriate medications and information for correct prescribing and administration in relation to age, physiological condition and body size of the child. Formulations developed specifically for children (authorised and age appropriate) are often needed.

Due to the lack of appropriate formulations, pharmacists and other healthcare professionals, parents or caregivers are often faced with the need to manipulate an adult medicine in a way that is not described in the *Summary of Product Characteristics* (SmPC). This manipulation can be, for example, breaking, crushing and cutting tablets. The practice and risks with regards to manipulations of dosage forms in children has 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 such medicines may expose children to overdosing and unintended side-effects or to underdosing and a reduction in efficacy and may also imply risks for healthcare givers such as exposure to toxic substances, for example, when handling cytotoxic drugs and inhaling powders from crushing tablets.

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 and access to child-specific medicines. A the same time, the *WHO Model List of Essential Medicines for Children* was first 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 WHA 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 against an accelerated timeline (*5*) . GAP-f has membership from 33 organisations, that span across its disease portfolio and operates across the product life cycle.

In 2024, at the seventy-seventh World Health Assembly, Member States recommitted to paediatric medicines and in a new resolution, entitled Accelerate progress towards reducing maternal, newborn and child mortality in order to achieve SDG targets 3.1 and 3.2, specifically call for renewed efforts and appropriate financing to accelerate investigation, development and introduction of better medicines for children (*6, 7*).

All together, these growing efforts are a testimony of 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 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.

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

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

acceptability. 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

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.

fixed dose combination. A combination of two or more active pharmaceutical ingredients in a fixed ratio of doses. This term is used generically to mean a particular combination of active pharmaceutical ingredients irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product.

flexibility. Dosage forms that are shown to be acceptable in the targeted paediatric population where a single unit strength or its multiples may be administered/given for achieving the intended therapeutic dose and effect. This approach can also apply for dosing of medicines in adults. Examples of flexible dosage forms are mini-tablets, orodispersible tablets, films, pellets and chewable tablets (if age-appropriate).

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.

orodispersible tablets. Solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.

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 drugs. Organ maturation, metabolic capacity, tissue and receptors maturation, and other factors such as development, may change with age, especially in early infancy (*9*).

The age groups identified by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (*10*) have been derived mainly from physiological and pharmacokinetic differences from birth to adulthood:

- preterm newborn infants;
- term newborn infants (0 to 27 days);
- infants and toddlers (28 days to 23 months);
- children (2 to 11 years);
- adolescents (12 to 16–18 years, dependent on region).

To facilitate additional context for the children age group (2 to 11 years), subgroups may be considered as pre-school or early childhood (2 to 5 years) and school-age or middle and late childhood (6 to 11 years).

Importantly, however, the choice of formulation for the paediatric population will be guided by factors not just necessarily aligning to these age classifications, such as the medical condition, acceptability of the dosage form, in addition to the dose in question. Therefore, the decision on the appropriateness of a formulation, and consequently any potential need for additional formulations, might need to be considered independently of these 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 formulation. 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 – as for adults – the balance of risks and benefits, taking into account 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 (*11 - 13*). Limitations, however, exist to the acceptability of different dosage forms in relation to the age and therapeutic needs, as well as the safety of excipients in relation to neonatal and paediatric development, as described by The European Medicines Agency (EMA) specific guidelines (*14, 15*).

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.

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 (such as, 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, development of sustained release systems).

Paediatric medicines should be affordable and factors that may influence the supply chain (for example, ease of transportation, ease of transportation and storage) should be considered as part of the drug development programs. Refrigeration is not always accessible to healthcare facilities and users.

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 chosen for the paediatric population is acceptable and appropriate for the target age to ensure adherence/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 like palatability, swallowability, tolerance and user friendliness. It is a multifaceted concept and depends on a variety of product characteristics such as:

- size/shape of oral medicines;
- dose volumes and needle size for injections;
- taste, smell and mouthfeel of oral liquid medicines;
- dosing and administration device;
- complexity of the handling required by the child or its caregivers prior to administration;
- clarity and accuracy of labelling information and directions for use;
- packaging.

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 reassure that the medicine is suitable for the targeted paediatric population. Different methodologies can be used to assess acceptability in the paediatric population (for example, questionnaires appropriately tailored, preference studies) or through more advanced modelling-based methods (1*6* - *19*). In-depth assessment of non-compliance during clinical trials could also provide useful insight on acceptability. Supportive data can be gathered from literature data, from adult panels, or from non-human sensory studies (for example, 'electronic tongue', rodent BATA models).

The acceptability considerations have necessitated availability of in vitro methods suitable for determining the properties of oral dosage forms such as their mouthfeel, texture, taste, and swallowability. In food engineering, in vitro 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. These 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. 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 starting from the early formulation development efforts by leveraging learnings in support of development of paediatric oral formulations (*20* -*27*).

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 tablets, opening capsules) 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 not being hampered through the revision of the composition.

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 product information. In addition, some of these tools can also be used as part of the clinical development of drugs (for example, when planning the acceptability studies).

As an example, The Royal College of Paediatrics and Child Health and the Neonatal and Paediatrics 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 utilisation of medical devices, etc.). These are tested resources and readily available for healthcare professionals, parents, carers and children to access (*28*).

Other work being adopted in clinical practice by healthcare facilities running paediatric clinics and used as part of clinical trials designs 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 that leads to positive results in the compliance with oral solid dosage forms and the reduction of liquid formulation needs (*29 – 32*). These practices should not prevent manufacturers from making every effort to address the needs for age-appropriate formulations in their development plan, but it should only be intended to support development plans where the age-appropriate formulations are totally unviable (for example, liquid or dispersible formulation).

Overall, the manufacturer should ensure that precise and clear information on the administration method is provided as part of the SmPC/Product Information to facilitate clear understanding at end-user level, so the medicinal product is administered as intended in the design

Note: More examples/cases to be sought from stakeholders during public consultation

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, and stability during manufacture, storage and use of the chosen dosage form (*33*). 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) and/or tuberculosis (TB). The development of fixed dose combinations may be more complex than for single compounds; guidance is provided in WHO guidelines (*34, 35*).

4.1 Quality

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

The acceptable level of impurities in APIs and degradation products in finished dosage forms should be qualified and controlled according to regulatory guidelines. 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 considered specifically 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*[1].

In vitro release testing

Guidance to dissolution testing have been outlined by the ICH (*36*) 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) (*37*). When dosage forms come with labelling instructions for optionally using soft foods and liquids to aid in their administration, dissolution drug release testing of the dosage form mixed with the proposed vehicle should be conducted (*38*).

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 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. High permeability can also be demonstrated using in vitro methods with Caco-2 cell systems. 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) and BCS class IV (low solubility, low permeability) (*39, 40*).

1 *The International Pharmacopoeia*, Geneva, World Health Organization (https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia).

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) (*40*). 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 (*41, 42*). 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 co-administered with juices and soft foods and this must be properly assessed as part of the development.

4.3 Excipients

The selection of excipients with appropriate safety and tolerability is 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 (*9*). Severe outcomes have been reported for excipients like benzyl alcohol, propylene glycol, and ethanol, but discussions on safety have also taken place for other excipients like azo dyes and propyl paraben. 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.

In the development of paediatric medicines, the number of excipients and their quantity in a formulation should be the minimum required to ensure an appropriate product with respect to performance, stability, palatability, microbial control, dose uniformity and other considerations necessary to support product quality.

The daily and cumulative excipient dose (mg/kg/day; mg/kg/treatment period), rate of administration (especially IV 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 consideration;
- regulatory status in the intended market.

Information on the safety of excipients can be found in resources such as *Safety and Toxicity of Excipients for Paediatrics "STEP database"*. Information and recommendations regarding intake are also available from food authority sources (for example, food legislations), however it should be kept in mind that such recommendations are valid only for the oral route, and often reflect life-long intake and a potentially different benefit/risk setting than for medicines. Guidelines such as *European Commission guidelines 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 propylparaben, sodium benzoate, propyleneglycol, benzylalcohol (*43 – 49*).

For many excipients though, 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. 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 nonclinical 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 established.

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

Falsified 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 and contaminants, manufacturers are alerted to take control measures to ensure the safety, purity and quality of such excipients and FPPs (*50, 51*).

Specific groups of excipients

Colouring agents

The use of colouring agents in paediatric medicines is generally discouraged, in particular in medicines for infants and young children. Their use may, however, be justified in certain cases, for example, to avoid accidental dosing errors in connection with medicines produced in several strengths. In this case, solid dosage forms like tablets and capsules may be preferred because size, shape and embossing can facilitate the identification of different strengths of the preparation. Additional use of colouring agents that match the flavour is discouraged unless this is necessary to disguise an unpleasant colour related to the API.

Some colouring agents used in paediatric medicines have been associated with hypersensitivity and allergic reactions. For some colouring agents, like 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, in paediatric formulations, they should be avoided wherever possible. The use of new preservative systems shall be justified and supported with data set on its safety profile. Sterile products and large volume parenterals intended for single use should not contain preservatives.

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 (ADI) of up to 10 mg/kg/day as the sum of methyl, ethyl and propyl paraben and their sodium salts (*44, 46*). A PDE (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.

Sodium benzoate is another commonly used preservative in oral liquid products. Safety concerns exist in neonates, specifically jaundice and metabolic acidosis, and is therefore not recommended in this age group. The ADI for adults and children above 4 weeks of age is 5 mg/kg/day (*47*).

Ophthalmic preparations without preservatives are strongly recommended for use in children, especially neonates. Therefore, preparations without preservatives should be developed wherever possible in order to cater for the diversity of patients' needs. When preservatives are required, their concentration should be of the minimum level consistent with satisfactory antimicrobial function in each individual preparation and a thorough justification for the choice of the preservative should be established. Ophthalmic preparations without any mercury-containing preservatives (for example, thiomersal) should also be considered.

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. 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 (*52*). 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. The latest guidance on sensory analysis has been published by EUPFI (*53*).

Sweetening agents may be either cariogenic or non-cariogenic. Attention should be paid to the following:

- It is important to ensure the safety of the sweetening agent in relation to specific conditions of the child (for example, diabetes, fructose intolerance, patients on a ketogenic diet).
- Avoid the use of aspartame in patients with phenylketonuria since it is a source of phenylalanine. Furthermore, aspartame should be avoided in infants less than 12 weeks old; the FDA and EMA have recommended a maximum dose 40 mg/kg/day (*54*).
- Sorbitol is a monosaccharide and, when ingested orally in large amounts, it can cause a laxative effect and gastrointestinal discomfort. The EMA recommends a maximum dose of 140 mg/kg/day for children and adults (*55*).
- Poorly absorbed or non-digestible sweeteners in high concentrations can cause a laxative effect.

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

An example of a "qualitative evaluation of the taste by a taste panel" for zinc formulations can be found in the United Nations Children's Fund (UNICEF)/WHO publication on production of zinc formulations (*56, 57*).

The severity of the condition to be treated must be considered, such as, whether a potential adverse reaction of the sweetening agent may be secondary to patient adherence.

<u>Solubility enhancers</u>

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 solubility enhancing

excipients, for example, the use of non-ionic surfactants and co-solvents such as glycerol, liquid macrogols and ethanol. If solubility enhancers are to be used, consideration should be given to the safety of both the agent and the formulation, for example, the risk of irritation and damage of intestinal tissues in neonates caused by hyperosmolality or other local toxicity. Risks associated with the use of solubility enhancers may be higher when they are included in parenteral preparations due to their exposure profile.

Ethanol should not be included in medicines for children without a clear demonstration of benefit. Although it is recognized that ethanol may not always be eliminated from FPPs, and replacements may raise other issues, the smallest possible amount should be used. When ethanol is used, adequate development data demonstrating that the lowest possible concentration of ethanol is used should be established. It is also recommended that manufacturers of existing formulations containing ethanol should consider reformulation if the medicine is intended for paediatric use.

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, limited clinical data and cases-reports. Children, specially under the age of 6 years, are more vulnerable to the effects of ethanol with higher peak ethanol blood concentrations observed than in adults for a similar intake. Likewise, reduced metabolic enzyme capacity in neonates might result in relatively higher exposure compared to older children. Adverse effects on the central nervous system are already evident at blood ethanol concentrations of 10mg/100mL in children. Also, in neonates, cutaneous absorption of ethanol is significant, and this may lead to local reactions and systemic toxicity. Chronic exposure to ethanol, even to small doses, is not recommended. Furthermore, ethanol presents a risk of interaction with other medicines.

Reflections on the safety of ethanol, including for children, and the thresholds for warning statements in the package information has been given by EC/EMA (*44, 45*).

The US FDA sets a maximum limit of ethanol as an inactive ingredient in oral over-the-counter products of up to 0.5% for children under 6 years; 5% for children 6 to 12 years; 10% for anyone 12

years of age and over (*58*). The EMA recommends blood ethanol levels not to exceed 1 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 6 years old and over (*44, 45*).

Propylene glycol is another cosolvent used in liquid preparations. Similarly to ethanol, it is metabolized by alcohol dehydrogenase and aldehyde dehydrogenase enzymes which do not fully develop until 4 years of age. Metabolic and neurological adverse effects have been reported with high amounts of propylene glycol used in paediatrics. The EMA have advised on safety limits of maximum daily amount of propylene glycol up to 1 mg/kg for neonates; 5 mg/kg for 1 month up to 4 years; and 500 mg/kg for 5 years and above; including adults (48). Note: see *List of examples of high-risk excipients and contaminants,* Appendix 2 of the *WHO good manufacturing practices for excipients used in pharmaceutical products* (under publication).

4.4 Packaging and labelling

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

- permit accurate dosing and convenient administration;
- 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.

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

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

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

Adequate information about the medicine and how to use it is important. Information about the dosage should be clearly spelt out, for example, as milligrams per 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.

5. Routes of administration

5.1 Oral/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/enteral administration depends on both age and clinical condition.

At the point of API design and excipient selection for the formulation, 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 (*59, 60*). In addition, the gastric emptying of sick newborns is most erratic and can be delayed. Further information can be found in an EMA guideline on medicines for term and preterm neonates (*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, mini-tablets or spherical granules (pellets), that allow production of dosage forms of varying strength, as well as different dosage forms like tablets and capsules, and dosage forms to be dispersed to form a liquid dose or to be sprinkled onto food. Platform technology has potential flexibility for manufacturing appropriate fixed-dose combination products. Breakable solid dosage forms specially designed to provide the appropriate dose may also serve the same purpose.

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 patient by mixing the dose with food or a beverage. Such mixing should not be encouraged unless it can be done in such a small volume that ingestion of the full dose can be guaranteed and if there are no undesirable physical or chemical interactions between the food and the medicine. If mixing with food or a beverage (including breast milk or formula milk) is foreseen, this eventuality should be evaluated by the appropriate compatibility studies. 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 Formulations Initiative (EUPFI) 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, mouthfeel) of the formulation throughout the development of the pharmaceutical product (*53*).

Administration through enteral feeding tubes

For neonates, seriously ill infants and children, as well as certain medical conditions, enteral administration of medicines via enteral feeding tubes is used and requires 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, any potential risk of adsorption of the API to the tube material, and potential interaction with feeds and other administered medicines. 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 as it will determine the volume of the dose that can be administered, and viscous drugs may lead to blockages of very narrow tubes such as the ones used in the neonatal population (4-8 French size).

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

Further information is provided in guidance from EMA and FDA (*61, 62*).

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 application to the mouth (chewable tablets, orally dissolving tablets or orodispersible tablets). Some are intended for swallowing after dissolution, dispersion in water or other suitable liquids. Their advantages over oral liquid preparations are improved physical and chemical stability, good dosage uniformity, lower amounts of potentially toxic excipients, 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 and/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 (< 6 months). It is necessary to identify appropriate product strengths and ratios of active ingredients for each medicine as well as to ensure that package sizes will allow optimal use under public health programmatic conditions.

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. 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 on to food, but this is not always appropriate (such as, due to taste issues or impact on bioavailability or specific considerations need to be given if containing enteric coated pellets or prolonged release granules where dispersion in fluid may be required avoiding crushing and dissolving). Instructions on the proper use of a capsule formulation should be provided on the label to facilitate correct administration.

Immediate-release tablets

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

Acceptability of tablets depends on the size of the tablet and the age of the child. 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 'mini-tablets') have emphasized the need for more flexible and scientifically based considerations, as more data emerges on acceptability related to size and 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 2 mm tablets (*63*), and small oblong tablets (2.5 x 6 mm) may be well accepted in infants and toddlers (*64*). More data for international guidance regarding acceptability on oral dosage forms and its potential risks (such as, choking, chewing) in small children as well as in older children and adolescents (such as, on their acceptance of large tablets/capsules) is still needed.

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

Alternative strategies to administer tablets should be considered by the manufacturer, for example, score lines to facilitate swallowing, as this will increase administration flexibility and therefore adherence or even exploring the role of structured education programmes on how to swallow tablets/capsules incorporated as part of the clinical trials and clinical development (see Education and Training section for details).

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 tablets scoring can be found in regulatory guidance documents such as the FDA (*65*) or *The International Pharmacopoeia*[2]. 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. Specially designed tablets and tablet punches may be needed.

If, however, score lines are intended to ease administration (and not to provide, for example, half dose) this should be clearly identified in the product labelling (*65*).

Caregivers often crush tablets to increase adherence. Crushing may, however, result in dosing inaccuracies, affect the bioavailability of some medicines, and may disclose poor-tasting APIs. The effect of crushing of tablets should be investigated by the manufacturer and this information should be provided in the patient information leaflet.

[2] *The International Pharmacopoeia*, Geneva, World Health Organization (https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia).

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/dissolving characteristics 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 6 months).

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

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 mini-tablets. A counting device may be necessary when a large number of pellets or mini- tablets is required.

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, and microcrystalline cellulose, which assists in obtaining a good mouthfeel and reduces grittiness. Other sweetening agents, such as sorbitol and xylitol suitable for direct compression, are also used.

A potential problem with chewable tablets is that they may be swallowed 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 is not to be drunk before effervescence has subsided in order to minimize ingestion of hydrogen carbonate. Effervescent tablets require continuous attention to levels of moisture and humidity during manufacture, packaging and storage.

The drawbacks of effervescent dosage forms are the need for clean water for dissolution and the ingestion of potassium or sodium 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 in water prior to administration. 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. 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 on the tongue 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 for several reasons. They may be acceptable to the same age groups as liquid preparations. In some situations, especially with younger children, the orodispersible dosage form may need to be dissolved in a small volume of liquid prior to administration.

Orodispersible tablets designed to disintegrate rapidly are prepared by compression of a formulation containing, for example, mannitol, a super-disintegrant, and a flavouring agent. The amount of API that can be incorporated depends on its physical properties. The product may be moisture-sensitive. Orodispersible tablets are flexible dosage forms, particularly well-suited for highly water-soluble APIs.

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) and fused deposition (melt extrusion) the most explored. As of 2024, levitracetam orodispersible tablets, produced by binder jetting, have been approved by the FDA. They are highly porous tablets that rapidly disintegrate with a sip of water and available in dose strengths of 250, 500, 750 and 1000 mg indicated for epilepsy in patients 4 years of age 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 (ODFs) 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.

However, they are not suitable for drugs that cause irritation. They are unstable in the buccal cavity and, since they are hygroscopic in nature, they require special packaging and offer a shorter expiration date (*66*).

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

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, hard capsules or in quickly disintegrating tablets, coated tablets and matrix tablets. Among the advantages of the sustained-release design is the reduced dosing frequency compared to conventional formulations of the same API, a feature which may improve adherence. 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 (*67*).

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 are included on the label.

B. Oral liquid formulations

Oral liquid preparations include aqueous solutions, suspensions, emulsions and syrups. They are most appropriate for children in the youngest age groups or patients with conditions who are unable to swallow solid dosage forms. The advantage of oral liquid preparations is that variable dose volumes can be measured and administered. The need for stabilizing agents (for example, antimicrobial preservatives, 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. Typical target dose volumes are 5 mL or less for children under 5 years and 10 mL or less for children of 5 years and older, 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. Special attention must be paid to the in-use stability of multidose preparations, both microbial and physicochemical.

Multidose preparations should, preferably, be packaged together with an appropriate dosing device. The correct graduation of the device and the accuracy of the volumes measured must be checked by the manufacturer. Generally, oral syringes are preferable because of the flexibility in dose measurement and superior accuracy compared to other devices such as graduated pipettes or plastic spoons. However, special consideration should be given when small volumes, <1 mL, are required since the accuracy of oral syringes can be variable depending on the dose volume size, particularly the variability increases if <0.25 mL (*68*). Information about the requirement of oral syringes graduation and the measuring of small volumes is described in the EMA Q&A Document (*69*).

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. Pre-filled oral syringes could also be considered although more costly.

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 minimised by choosing the suspending agent 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 that 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 containers that can hold the reconstituted multidose preparation. The liquid vehicle can be provided together with the dry preparation, especially when the product is intended for markets where access to clean water may be difficult. Manufacturers should provide clear instructions on how to reconstitute the product, for example, with boiled and/or cooled water, in the product information.

However, these types of formulations present some disadvantages such as being packaged in larger containers (such as, bottles) making the transport more challenging and requiring antimicrobial agents for stability purposes since most of them are multidose preparations.

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/ 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 risks of dosing errors (for example, risks of confusion on calculating the number of drops required for a given dose, or if a dose requires several drops that carers are not at risk of making a mistake counting the drops at the time of administration). The in-use performance of the dose-measuring device 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 (*70, 71*).

Sustained release formulations, liquid

Ion-exchange resin sustained release formulations have recently been developed that provide biphasic drug release profiles in liquid dosage forms. Resins are typically <500 µm in diameter and can be composed of sodium polystyrene sulfonate to which ionizable drugs are ionically bound. Typically, 30% of the drug is non-ionically bound allowing immediate release, while 70% of the drug is ionically bound to the resin and the resin-drug complex is coated with water-insoluble polymer. Sustained drug release arises as ions from the gastrointestinal lumen exchange with the drug ionically bound to the resin. Sustained release preparations of ion-exchange resins have been approved for methylphenidate formulations indicated for attention deficit hyperactivity disorder and provide the added advantage of taste masking.

5.2 Rectal administration

Rectal administration is an important route that can be used for both local (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 contents in the rectum may unpredictably delay absorption.

Dosage forms for rectal administration are primarily suppositories, rectal capsules and rectal liquids (enemas). Other dosage forms are available, 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 healthcare 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 but it depends 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 which can be cut in 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 acceptability of cutting should be studied as part of the product development.

Two types of suppository base are available: base insoluble in water (such as, hard fat) which melts below body temperature and a base soluble or miscible with water, for example, macrogols, which are dissolved in or mixed 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, 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 pre-filled syringes equipped with a rectal tube facilitates individual dosing and may reduce the need for several strengths of the formulation.

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

5.3 Parenteral administration

Parenteral administration refers to the administration of medicines via the Intravenous, intramuscular or subcutaneous routes.

Commonly these routes of administration require the parenteral drug being administered using syringes and needles. Most children have a fear of injection needles and, in some circumstances (depending of drug, condition, etc.), there are possible alternatives that prevent multiple injections, for example, in the case of long treatment durations. Another example, needle-free injection devices (jet injectors) that drive small droplets through the skin by high pressure, could be considered for subcutaneous administration. However, experience of their use in paediatric populations, especially in smaller children, is limited.

When the IV route is required, catheters and injection ports that can remain in place for the length of the treatment can also prevent the need of repeated injections.

Sometimes sustained release formulations to be administered Intramuscularly or subcutaneously also help to reduce the number of injection but this approach requires consideration of blood perfusion patterns in different childhood ages.

General parenteral formulation design aspects

Aqueous preparations (solutions or suspensions) must be adapted to the physiological conditions on the application site. The tolerances for deviations in pH and osmolality are dependent on the route of administration. Hyperosmolar and/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 on to the surfaces of plastic containers and catheters, and to leaching of plasticizers from containers and catheters to the parenteral preparation. 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).

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 (volumes, diluents, etc.) are clearly described in the product information. Information on the size of syringe that permits accurate administration would be helpful too.

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

In the case of the intravenous or subcutaneous administration, if the medicinal product is likely to be co-administered using the same line as other treatments, compatibility issues with concurrent medication should be studied (such as, other IV medication through the same line including Total Parenteral Nutrition, or even mixed in the same syringe as it is the case in drugs administered via the subcutaneous route in palliative care, for example).

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

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. Target volumes and electrolyte contents are important for all paediatric patients, however, these are critical for neonates (*72*).

Specific points to consider for administration of IV parenteral preparations

Often the intravenous drugs are administered as infusions. 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 mmoL prescribed and mg on the label; conversion between mg prescribed and percentage concentration on the label; and decimal points) should be avoided to prevent errors in preparation and administration of IV drugs. In general, medicines administered as IV infusions are considered high

risk drugs and complex calculation processes are directly involved with a high incidence of medication errors.

If calculations are required, for example, dose/kg/hr converted to mL/hr to administer using an infusion device, information on how to do it should be provided and, if possible, a standardization approach should be considered such as, weight banded standard concentrations aided by the use of pre-programmed pumps that calculate the infusion rate rather than bespoke per individual patient weight concentration (*73,74*).

Infusions are administered via catheters, specifically for neonates, consideration must be given to 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.

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 for their use such as, electricity supply or technical support (*75 - 77*). The provision of tables using the standard concentrations and calculating the drops required for dosing via droppers can provide significant support to healthcare staff and prevent errors.

The need for additional steps in the preparation of the product for administration should be minimized, for example, by developing ready-to-use preparations. The measurement of volumes smaller than 0.1 mL should not be required as this is not possible to measure accurately in clinical practice. Dose volumes in hundredths of a millilitre should be avoided. Tables should be included in the product information clearly stating the dose and the volume to be measured, and how this can be achieved safely and accurately.

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

Consideration to the child's fluid and electrolyte balance contribution of the diluted product should be given in addition to the volume and/or electrolyte content of the formulation prior to dilution, which is especially important in neonates as it can provide a significant amount of their daily allowances.

Intramuscular/subcutaneous routes

Some parenteral preparations are administered by the subcutaneous and intramuscular routes, for example, vaccines. The limited muscle mass of newborns and, in particular, of preterm infants, constrains the use of intramuscular injections. 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 to the subcutaneous bolus injection volume should be considered, volumes of injections must be kept to the minimum possible. 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 absence of data, hence, injection volumes should be kept lower than above where possible or otherwise appropriately justified (*78*).

Drugs can also be administered via SC infusion where larger volumes can be administered over time. Some considerations on infusions compatibilities and catheters used were already discussed under General parenteral formulation aspects.

5.4 Dermal and transdermal administration

Dermal

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

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

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

Transdermal patches

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

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

When designed to be cut, information on the cutting technique should be provided 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.

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 implications of the physiology of children of different ages and their ability to use the devices correctly should be considered in the development of paediatric inhalations (*79*). Depending on their age, children may have more or less difficulty with some of the devices. Problems with the coordination of the inhalation for MDIs and the ability to inhale strongly enough for DPIs determine the effectiveness of getting the medicine into the lung.

The total lung deposition is important for the clinical efficacy of preparations for inhalation. Generally, it is affected by the formulation and delivery device controlling size distribution of the aerosol and patient-related factors such as the current disease state. The diameter of the airways is smaller in children than in adults; hence deposition by impact in the upper and central airways may be significantly higher in children (*80*). The particle size of the aerosol produced by the delivery device needs to be explored during development.

Nebulized liquids are potentially suitable for young children who cannot use MDIs and DPIs. Their use, however, requires nebulizing devices and access to electricity.

MDIs may be suitable for children from birth when combined with a spacer. A spacer eliminates the need for coordinating the MDI actuation and the start of inhalation. For children younger than 2–3 years, a facemask is also required. This can be replaced by a mouthpiece when the child is able to manage the system.

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

5.6 Intrathecal/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 antibiotics, antineoplastic, analgesic and antispasticity drugs have been administered directly into the cerebrospinal fluid (CSF). Analgesic and antispasticity drugs are administered intrathecally into the CSF surrounding the spinal cord and the ICV route is preferred for antibiotics and antineoplastic drugs because administration via this route ensures a more homogeneous drug distribution throughout the CSF space, via Omaya reservoirs for repeated access

or catheters insertions for single use. The pH of solutions and buffering excipients need to be carefully selected for isotonicity, as well as flushing techniques with CSF fluid (81, 82).

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

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Annex 1

Note: Proposal to develop an annex that contains visual information comparing advantages and disadvantages of routes of administration layered with advantages and disadvantages of different dosage forms from a "manufacturability" perspective and from and end user perspective;