DEVELOPMENT OF PAEDIATRIC MEDICINES:
PHARMACEUTICAL DEVELOPMENT.
POINTS TO CONSIDER

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

This paper has been prepared by Professor Henning G. Kristensen, Denmark, and presents a first draft on pharmaceutical development of paediatric medicines. It is based on the above-mentioned paper and the European Medicines Agency (EMEA) Reflection Paper: Formulations of Choice for the paediatric population (2006).

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

Please address comments on this proposal, by 13 May 2008, to Dr S. Kopp, Quality Assurance and Safety: Medicines, Medicines Policy and Standards, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int with a copy to bonnyw@who.int.
SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/08.257: DEVELOPMENT OF PAEDIATRIC MEDICINES: PHARMACEUTICAL DEVELOPMENT. POINTS TO CONSIDER

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tbody>
<tr>
<td>First draft points for consideration prepared by Dr Susan Walters, Australia</td>
<td>14 May 2007</td>
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<tr>
<td>Further extended revision of the part on pharmaceutical development as a stand-alone text</td>
<td>February 2008</td>
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<tr>
<td>Circulation of document for comments as well as posting on Expert Committee and Prequalification web sites</td>
<td>March-April 2008</td>
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<tr>
<td>Consolidation of comments and review in informal consultation</td>
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<td>Circulation of revised draft for comments</td>
<td>July 2008</td>
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<td>13-17 October 2008</td>
</tr>
</tbody>
</table>
CONTENTS

1. INTRODUCTION .......................................................................................... 4
2. AGE CATEGORIES IN PAEDIATRIC POPULATIONS .............................. 4
3. DOSAGE FORMS OF CHOICE ............................................................... 5
4. ACTIVE PHARMACEUTICAL INGREDIENTS ........................................ 7
   4.1 Purity of APIs .................................................................................. 9
   4.2 Aqueous solubility ........................................................................ 9
   4.3 Stability aspects ............................................................................. 10
   4.4 Microbial purity ............................................................................ 10
5. EXCIPIENTS ............................................................................................ 10
   5.1 Choice of excipients ..................................................................... 11
   5.2 Safety aspects .............................................................................. 12
   5.3 Taste masking of oral liquids ........................................................ 14
   5.4 Colouring agents .......................................................................... 15
6. PHARMACEUTICAL DEVELOPMENT .................................................. 15
   6.1 Design of dosage forms ............................................................... 17
   6.2 Dissolution testing ....................................................................... 18
7. ORAL ADMINISTRATION ....................................................................... 18
   7.1 Biopharmaceutical parameters ..................................................... 19
   7.2 Liquid oral dosage forms ............................................................... 19
   7.3 Solid oral dosage forms ................................................................. 21
8. RECTAL ADMINISTRATION .................................................................. 22
9. INJECTABLES ......................................................................................... 24
10. REFERENCES ......................................................................................... 25
1. INTRODUCTION

Safe and effective pharmacotherapy in paediatric patients requires the timely development of information on the proper use of medicines in paediatric patients of various ages. Formulations developed specifically for the paediatric population are often needed.

The use of unlicensed and off-label medicines in children is, however, widespread. According to some authorities, more than 60% of all medicines used in children have not been tested in or authorized for the paediatric population. Such testing as has been conducted in adults may have been for a different indication. Adult dosage forms may not be suitable for use in younger children because their physiology, metabolism, pharmacokinetics and pharmacodynamics may be quite different from those of adults. This lack of information and frequently a lack of appropriate dosage forms may expose children to overdosing and unwanted side-effects, or underdosing without the expected efficacy.

A separate issue is that of extemporaneous preparation of medicines from starting materials or adult medicines. Pharmacists are often faced with the need to extemporaneously manipulate adult medicines or active pharmaceutical ingredients (APIs) to provide medicines for paediatric use. The practise is hazardous, both for the patient in terms of product stability, bioavailability and accurate dosing, and for the dispenser who may face ethical and legal consequences in the event of a poor outcome when the product is administered. Whilst recommending against off-label manipulation whenever possible, this paper provides guidance for situations where there are no other options.

In pharmacology and clinical paediatrics the focus is on the API when determining the dosage, clinical effects and adverse drug reactions. The formulation of paediatric medicines is also important since the choice of dosage form and its formulation determine, in practice, whether the dose can be successfully delivered to the patient.

This paper is intended to provide guidance on the formulation of paediatric medicines to be prepared extemporaneously or intended for a marketing authorization. The guidance focuses on suitable dosage forms for children of different ages, formulation excipients and some specific dosage forms.

2. AGE CATEGORIES IN PAEDIATRIC POPULATIONS

This paper uses the following age groups in relation to developmental stages:

- pre-term newborn infants/"premature" (< 37 weeks gestation);
- full-term newborn infants/"neonates" (0-28 days);
- infants and toddlers (1 month to 2 years);
- children, pre-school (2-5 years);
- children, school (6-11 years); and
- adolescents (12 years to legal age of consent (16 or 18 years dependent on the region)).

The age categories adopted by the International Conference on Harmonisation (ICH) (ICH E11, Clinical Investigation of medicinal products in the paediatric population) combine children from 2 to 11 years into one group. For the present purpose it is appropriate to subdivide this group into two: pre-school (2-5 years) and school (6-11 years), because of the differences in the children's ability to accept and use different dosage forms (see table 3.1).
Paediatric medicines must allow accurate administration of the dose to children of varying age and weight and, at the same time, the formulation and the manner in which they are administered must be acceptable to the child and the care-giving adult.

Information on developmental physiology and paediatric pharmacokinetics and pharmacodynamics is provided in the WHO Model List of Essential Medicines for Children (First List, October 2007). The essence of this information is that there may be no single formulation, which is ideal for paediatric patients of all ages, such that a range of dosage forms in the portfolio would be preferable.

3. DOSAGE FORMS OF CHOICE

There is limited knowledge available on the acceptability of different dosage forms, administration volumes, size of unit dosage, taste and the acceptability and safety of excipients in relation to the age and development status of the child. Some guidance on these aspects is provided in the European Medicines Agency EMEA Reflection paper: Formulations of choice for the paediatric population (EMEA/CHMP/PEG/196810/2005). Ernest et al. published a review article in 2007 on the needs and challenges in developing paediatric medicines (J. Pharm. Pharmacol. 2007, 59:1043-1055).

Table 3.1 presents a rough guide on preferred dosage forms in relation to age. The table is extracted from a similar table in the above-mentioned EMEA Reflection Paper. It is not an in-depth, evidence-based table, but is based on a questionnaire for hospital paediatricians, pharmaceutical scientists and parents. Thus, the table reflects some general aspects of acceptability of various dosage forms. This is a field where research is needed so the table should not be taken as a strict recommendation for the development of a specific dosage form for an age group.

The entries marked by an asterisk (*) in Table 3.1 indicate that for children up to 2 years, the dosage form has a good applicability, and for children of 2 years and above that the dosage form passes the preferred acceptability or is the dosage form of choice. Parents and adult caregivers are responsible for administering medicinal products to many paediatric patients. This is in particular valid for the lower age groups where the children do not make their own decisions as to acceptable dosage forms. The opinion of the caregiver and the ease of administration must be taken into account. For the higher age groups the child’s acceptance and the convenience of administration influence the question on the dosage form of choice.

During childhood there are significant changes in the ability to handle different dosage forms. Small-volume liquid medicines are appropriate for use in the younger age groups. Liquid medicines including effervescent and fast-dissolving orodispersible formulations are suitable for most ages, while tablets and capsules are more convenient to the lifestyle of adolescents. The age at which children can swallow intact capsules and tablets is highly dependent on each individual and on the training and support they receive from health-care professionals and caregivers. It has been suggested that children of less than 6 years can learn to take solid dosage forms, particular for chronic therapy or when faced with unpalatable liquids as an alternative. Dosing of multiple mini-tablets may be preferred over a single larger dosage form and can allow dosing flexibility. Problems with swallowing may be overcome by scoring of tablets allowing breakage into halves or quarters, by development of chewable tablets, dispersible tablets, effervescent tablets or dosage forms that melt on the tongue.
Seriously ill children will require injections. For less serious illness and long-term administration the oral route is preferable but other routes such as rectal or transdermal administration can be useful.

Table 3.1. Dosage forms of choice. Extract from EMEA Reflection Paper: Formulations of choice for the paediatric population (2006)

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Pre-term newborn infants</th>
<th>Full-term Newborn infants (0-28 days)</th>
<th>Infants and toddlers (1 month to 2 years)</th>
<th>Children pre-school (2-5 years)</th>
<th>Children school (6-11 years)</th>
<th>Adolescents (12 to 16/18 years)</th>
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<tbody>
<tr>
<td><strong>Oral route:</strong></td>
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<tr>
<td>Solutions/drops</td>
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<tr>
<td>Emulsions/suspension</td>
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<td>Effervescent forms</td>
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<td>Powder/granules</td>
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<td>Tablets</td>
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<tr>
<td>Capsules</td>
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<tr>
<td>Orodispersible forms</td>
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<tr>
<td>Chewable tablets</td>
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<td><strong>Nasal route:</strong></td>
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<tr>
<td>Nasal solutions/drops</td>
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<tr>
<td>Semi-solids</td>
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<tr>
<td><strong>Rectal route:</strong></td>
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<tr>
<td>Suppositories</td>
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<tr>
<td>Enema</td>
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<tr>
<td>Rectal capsules</td>
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<td><strong>Dermal application:</strong></td>
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<tr>
<td>Semi-solids</td>
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<tr>
<td>Liquid forms</td>
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<tr>
<td>Transdermal patches</td>
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<td><strong>Parenterals:</strong></td>
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<tr>
<td>i.v. administration</td>
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<tr>
<td>i.m. administration</td>
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<tr>
<td>s.c. administration</td>
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<td>*</td>
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<tr>
<td>Pump systems</td>
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<tr>
<td><strong>Inhalation:</strong></td>
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<tr>
<td>Nebuliser</td>
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</tr>
<tr>
<td>MDI/spacer</td>
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<td>*</td>
</tr>
<tr>
<td>DPI</td>
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<tr>
<td><strong>Ocular route:</strong></td>
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<tr>
<td>Eye drops</td>
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<td>*</td>
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<tr>
<td>Semi-solids</td>
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</tbody>
</table>
Particular problems in the medication of children include:

- acceptability in terms of organoleptic properties (taste, colour, odour), nature of packaging and pack design including emblems, pictures and drawings;
- size and shape of solid oral dosage forms;
- the need to vary the dose according to age, body weight and/or surface area; and
- the acceptability of the product and its packaging to caregivers.

Taste is the most important factor governing the acceptability by the child of oral dosage forms. Unpleasant tasting APIs do not usually give rise to problems when formulated as solid oral dosage forms as the dosage form is film- or sugar-coated and can be swallowed intact. However, palatability may need improvement in some tablets, i.e. effervescent, soluble and dispersible tablets, that are intended to be dissolved or dispersed in water before swallowing, and chewable tablets and tablets to be placed in the mouth (buccal tablets, sublingual tablets). Taste masking and flavouring of liquid oral dosage forms are highly important for a child’s acceptance of the medicine and hence for compliance, even in cases where the adult patient would accept the non-taste-masked medicine.

Mixing of medicines with food may improve palatability and compliance, e.g. use of “sprinkle” capsules or mini-tablets. Mixing with food may, however, alter the stability and absorption profile. The compatibility of the product with particular types of food should, therefore, be tested by the manufacturer and detailed in the prescribing information.

In general, medicines should be convenient to use, elegant and stable. Because the dose varies in the paediatric population, products that allow the dose to be varied are an advantage, e.g. liquid dosage forms administered by a graduated dropper, and mini-tablets that can be administered as multiple units.

The present paper focuses on the following dosage forms that are commonly used in paediatrics:

- solid dosage forms for oral administration;
- liquid dosage forms for oral administration;
- suppositories and enemas; and
- injections.

According to Table 3.1 there are other dosage forms suitable for children whose cost may preclude them from use in less developed regions, e.g. transdermal patches, pressurized metered dose inhalers (MDIs) and dry powder inhalers (DPIs). Discussion of these and other dosage forms can be found in the EMEA Reflection Paper: Formulations of use for the paediatric population (2006).

4. ACTIVE PHARMACEUTICAL INGREDIENTS

Prior to the development of pharmaceutical dosage forms it is essential that certain fundamental physical and chemical properties of the API are determined experimentally in the laboratory or established by literature studies. This first learning phase is known as preformulation comprising analytical preformulation and API characteriZation. Table 4.1 outlines the elements of a typical preformulation study.
### Table 4.1. Main elements of a preformulation study

<table>
<thead>
<tr>
<th>Analytical preformulation</th>
<th>Analytical methods to determine identity, purity and assay of the API</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>API characterization</strong></td>
<td></td>
</tr>
<tr>
<td>A. Chemical properties</td>
<td></td>
</tr>
<tr>
<td>1. Solubility</td>
<td>1. Aqueous solubility profile, pH 1 – 8</td>
</tr>
<tr>
<td>2. Dissociation constant</td>
<td>2. pK&lt;sub&gt;A&lt;/sub&gt;</td>
</tr>
<tr>
<td>3. Apparent partition coefficient</td>
<td>3. Partition between lipidic solvent (usually n-octanol) and water; pH effect</td>
</tr>
<tr>
<td>4. Melting point</td>
<td>4. e.g. capillary melting, differential scanning calorimetry</td>
</tr>
<tr>
<td>5. Crystal properties</td>
<td>5. e.g. X-Ray diffraction, thermal analysis, FTIR</td>
</tr>
<tr>
<td>6. Density</td>
<td>6. True density</td>
</tr>
<tr>
<td>7. Hygroscopicity</td>
<td>7. Sorption/desorption isoterms</td>
</tr>
<tr>
<td>B. Physical properties of the bulk material</td>
<td>8. e.g. sieve analysis, light microscopy, laser diffraction</td>
</tr>
<tr>
<td>8. Particle size distribution</td>
<td>9. Particle shape, crystal habit, surface area by e.g. gaspermeametry</td>
</tr>
<tr>
<td>9. Surface properties</td>
<td>10. Dissolution rate</td>
</tr>
<tr>
<td>10. Dissolution rate</td>
<td>11. Contact angle water/solid substrate</td>
</tr>
<tr>
<td>11. Wettability</td>
<td>12. Bulk and tapped density, flow rate</td>
</tr>
<tr>
<td>12. Packing properties, flowability</td>
<td>13. Ability for form a compact by compression</td>
</tr>
<tr>
<td>13. Compactability</td>
<td></td>
</tr>
<tr>
<td>C. Other quality attributes</td>
<td></td>
</tr>
<tr>
<td>15. Odour, taste</td>
<td>18. Screening of mixes of API and potential excipients</td>
</tr>
<tr>
<td>16. pH of saturated solution</td>
<td></td>
</tr>
<tr>
<td>D. Stability</td>
<td></td>
</tr>
<tr>
<td>17. Chemical and physical stability</td>
<td></td>
</tr>
<tr>
<td>18. Compatibility with excipients</td>
<td></td>
</tr>
</tbody>
</table>

The relative importance of the properties listed in Table 4.1 depends on the dosage form and its intended route of administration. Some aspects of the chemical and physical properties of APIs are discussed in the sections on specific dosage forms. For further information on preformulation testing, reference is made to pharmaceutical literature and textbooks, for example JI Well: Pharmaceutical Preformulation, Ellis Horwood, 1998, and ME Aulton (Ed.): Pharmaceutics, The Science of Dosage Form Design, Chapter 8, Churchill Livingstone, 2002.
4.1 Purity of APIs

Guidelines regarding the acceptable content of impurities in new APIs are provided in the *ICH Q3A (2R) guideline: Impurity Testing. Impurities in New Drug Substances*. The principles of this guideline may be adapted to existing APIs.

Impurity specifications for off-patent APIs can usually be found in pharmacopoeias, e.g. *The International Pharmacopoeia* (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the United States Pharmacopeia (USP) and the Japanese Pharmacopoeia (JP). Pharmacopoeia standards for impurities are based on limit testing with limits for the individual impurities that have been qualified either by the licensing authorities based on the reported clinical trials, or by long-term usage. Standards of the Ph.Int. and the Ph.Eur. list impurities that are known to be present or potentially present in the API.

Instructions and impurity limits in both the ICH guideline and pharmacopoeia standards are related to adults. There is no information available at present on impurity control in relation to children, in particular whether the qualified concentrations in specific APIs are also acceptable to children.

4.2 Aqueous solubility

Dissolution of the API in the body fluids is a prerequisite to the pharmacological action of both local acting and systemic acting dosage forms. The saturation solubility of the API in water and the dissociation constant ($pK_A$) are important characteristics that must be known prior to formulation of a dosage form. Solubility dictates the ease with which solutions such as oral liquids and injections can be formulated. Knowledge about $pK_A$ allows the use of pH adjustment to improve aqueous solubility and, thereby, within the acceptable pH-range to reduce the unit dose volume. It assists in the selection of a proper salt form for a poorly soluble acid or base to improve bioavailability of solid oral dosage form. Generally, salts of strong acids like hydrochloric acid are soluble within a wider pH-range than the salts of weak acids but it should be borne in mind that the pH of, for example, a hydrochloride, is lower than the pH of, for example, a tartrate and, therefore, likely to be more irritating in the gastrointestinal (GI)-tract.

Solid oral dosage forms intended for systemic action must release the API into the GI-fluids prior to absorption. According to Kaplan (Drug Metab. Rev., 1972, 1:15-32) potential bioabsorption problems may occur unless the API has an aqueous solubility in excess of 1% (10 mg per ml) over the pH range 1 to 7 at 37 °C. A solubility of less than 1 mg/ml indicates the need for solubility enhancing methods in the formulation of solid oral dosage forms, e.g. formation of complexes with excipients like cyclodextrins. Aqueous solubility is generally proportional to dissolution rate. It is, however, possible to increase the dissolution rate by, for example, particle size reduction of the API or addition of surfactants that improve wetting and dispersion into the GI-fluids.

These considerations apply to APIs that have a high permeability across the gut wall, i.e. Classes I and II in the Biopharmaceutical Classification System. Information on the classification of WHO essential medicines is provided by Lindberg et al. (Eur.J.Pharm.Biopharm., 2004, 58(2):265-278).
4.3 Stability aspects

By investigating the chemical and physical stability of the API it is possible to advise on formulation approaches and indicate types of excipients, specific protective additives and packaging which are likely to improve the integrity of the API and the final drug product.


Stress testing generally provides an understanding of:
- likely routes of degradation in finished products;
- whether protective excipients are needed in the formulation, such as antioxidants; and
- evaluation of the specificity of analytical methodology for the intact API and its degradation products.

Stress testing should include an evaluation of the physical stability of a solid, particulate API, e.g. the risk for changes in crystal properties and particle size when the API is exposed to thermal and mechanical stresses (WHO working document QAS/06.179: Draft stability testing of active pharmaceutical ingredients and pharmaceutical products).

4.4 Microbial purity

In order to meet recommended criteria for the microbial purity of pharmaceutical dosage forms (Ph.Int. Fourth Edition, Methods of analysis, Section 3.1) and to meet good manufacturing practice (GMP) requirements, consideration should be given to the contamination level of starting materials (APIs and excipients).

5. EXCIPIENTS

An excipient is defined as any component other than the claimed therapeutic ingredient or ingredients that are present in the finished dosage form to be taken by or administered to the patient. The chemical, physical and microbial properties of a drug product are directly affected by the nature of the excipients, their concentrations and interactions with the API and with each other. In many cases, the excipients make up the major proportion of the unit dose. Consideration should, therefore, be given to the possible presence of more or less toxic impurities in excipients, for example, deliberately added stabilizers such as antioxidants in lipidic excipients, residues of organic solvents originating from a chemical transformation to confer special characteristics to the excipient, or residues of foreign substances like pesticides in lanolin and mycotoxins in certain herbal products.

Excipients may be a single chemical entity. Many excipients of natural or semi-synthetic origin are mixtures of chemically related components, for example, polyol esters being a mixture of mono-, di- and triesters. Furthermore, mixtures of excipients that are ready-for-use preparations are marketed for, e.g. direct compression purposes or for film-coating.

Excipients can be classified according to their intended function in the dosage form:
● Optimization of chemical or physical stability, e.g. agents for pH adjustment and buffering, stabilizers for suspensions and emulsions, antimicrobial agents, antioxydants.

● Optimization of the biopharmaceutical profile of the dosage form, e.g. tablet disintegrants and binders, polymer coats to adjust the rate of release.

● Excipients to enhance the manufacturability of the dosage form, e.g. fillers for tablets and capsules, tablet lubricants and glidants.

● Improvement of the patient acceptability of the dosage form, e.g. sweetening agents, colouring and flavouring agents.

Some excipients, in particular polymers of natural or synthetic origin, are multifunctional, i.e. they have different functions in different dosage forms. For example, methylcellulose may be used to increase the viscosity of aqueous liquids for stabilization of dispersions, as a film former in tablet coats, and as a matrix former in modified-release tablets and capsules. For further information, consult, e.g. the *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press (2006).

### 5.1 Choice of excipients

The initial selection of excipients for a dosage form should consider:

- the route of administration and the chosen dosage form
- the desired delivery characteristics
- published formulations
- the formulation chemist’s previous experience with other products of similar nature and personal knowledge of suitable formulations
- known compatibilities and incompatibilities of the API with common excipients.

The choice of excipients for a dosage form is limited to such materials that have been properly evaluated for their safety, either directly by a procedure like the one described in USP, *Excipient Biological Safety Evaluation Guidelines*, or by bibliographic means. For the present purpose this means that the choice of excipients should generally be restricted to well known excipients used in already marketed products, intended for the same route of administration. Some guidance to this effect can be found in the United States Food and Drug Administration's *Inactive Ingredients Guide*. This guide was published in 1995 but does not fully reflect the range of possible excipients. Another source is *Japanese Pharmaceutical Excipients*. General information on the uses of common excipients and their known incompatibilities are provided in the *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press. Information on excipients in marketed products can be found in the summary of product characteristics (SPCs) published on drug regulatory authority web sites but without any detailed information on the functions of the excipients in the drug product.

The objective of API-excipient compatibility studies is, in the early stage of the development work, to identify possible interactions between the potential formulation excipients and the API. Rapid screening for possible interactions are frequently done by differential scanning calorimetry (DSC) analysis of 1:1 mixes of API and excipient. However, the data obtained require skilled interpretation and may be misleading; false positives and negatives are not unusual. A more
A laborious approach is to store the binary mixes at specific humidities at accelerated conditions and analyse by a stability indicating method, typically liquid chromatography.

Screening for API-excipient compatibility does not mean that the choice of excipient is safe from a stability point of view. Chemical incompatibilities may arise in the final multicomponent formulations. Possible interactions have to be investigated as a part of the stability studies on the final dosage form.

5.2 Safety aspects

Safety data on excipients determined by animal safety testing are usually referenced for use in adults and are not necessarily applicable to their use in children. In many cases adverse effects concern the risk of irritation and allergic reactions following local application of a dosage form, especially administration to the eye and the skin. Some information is provided in the EU guideline: *Excipients in the label and package leaflet of medicinal products for human use* (2003) and in the *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press (2006). With regard to the paediatric population special attention should be paid to toxic risks associated with antimicrobial preservatives, antioxidants and colouring agents, even when used in concentrations acceptable in adults.

The safety of excipients in children is not well documented. Information on some excipients is given in Table 5.1 but it should be noted that this information is not exhaustive.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Typical function</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almond oil</td>
<td>Emollient in skin-care products</td>
<td>Has been shown to cause contact dermatitis in dermal application for prolonged periods</td>
</tr>
<tr>
<td>Aspartam</td>
<td>Sweetener</td>
<td>May be harmful for patients with phenylketonuria. May cause behavioural abnormalities in children (dose greater than?)</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>Antimicrobial preservative</td>
<td>May cause toxic reactions and allergic reactions in children up to 3 years old. Must not be given to neonates</td>
</tr>
<tr>
<td>Benzoic acid and salts hereof</td>
<td>Antimicrobial preservative</td>
<td>When used parenterally, they may increase the risk of jaundice in newborn infants</td>
</tr>
<tr>
<td>Carageenan</td>
<td>Suspending agent</td>
<td>Known to induce inflammatory responses in animals. Should not be given to children</td>
</tr>
<tr>
<td>Colouring agents</td>
<td></td>
<td>Concerns on the safety profile of colorants in pharmaceuticals and foods are associated with hypersensitivity and hyperactivity, especially in children. This is valid, in particular, for azo colouring agents (e.g. tartrazine, sunset yellow, azorubine/ carmoisine, amaranth, poncheau 4R red/cochineal red A, brilliant black BN) and other synthetic colorants; tartrazine should not be used in paediatric medicines</td>
</tr>
<tr>
<td>Diethylene glycol</td>
<td>Solvent</td>
<td>Toxic in oral formulations</td>
</tr>
<tr>
<td>Substance</td>
<td>Type</td>
<td>Use and Comments</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Docusate sodium</td>
<td>Surfactant, wetting agent</td>
<td>Used therapeutically for faecal softening and laxative properties; in children over 6 months old up to 75 mg, in divided doses, is used. Use of docusate sodium as an excipient in oral preparations should therefore be avoided in the lower age groups, or for the higher age groups the quantity should be controlled to avoid diarrhoea.</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Solvent, co-solvent</td>
<td>In larger doses, may cause various adverse symptoms. For the paediatric population the maximum of ethanol is: - 0.5 % for children under 6 years - 5 % for children 6-12 years - 10 % for children over 12 years.</td>
</tr>
<tr>
<td>Glycerol (glycerine)</td>
<td>Solvent, humectant, emoillient</td>
<td>Has to meet the standard of Ph.Int. to limit contamination with diethylene glycol. In large doses, a mild laxative. When used in acceptable quantities glycerol is an acceptable excipient.</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>Skin softener. Preservative in oral formulations</td>
<td>Newborn children have difficulty metabolizing the R-enantiomer. Neither the R-enantiomer or the racemate should be used in children less than 3 months old.</td>
</tr>
<tr>
<td>Lactose</td>
<td>Filler in tablets, capsules and lyophilized products</td>
<td>Concern about lactose intolerance.</td>
</tr>
<tr>
<td>Liquid paraffin (mineral oil)</td>
<td>Skin emollient, lubricant in oral, solid formulations</td>
<td>May cause lipoid pneumonia when inhaled.</td>
</tr>
<tr>
<td>Arachis oil (peanut oil)</td>
<td>Solvent in parenterals, vehicle in dermal preparations</td>
<td>May lead to episodes of hypersensitivity. Risk for nut allergies.</td>
</tr>
<tr>
<td>Polysorbates (polyoxyethylene sorban fatty acid esters)</td>
<td>Surfactants, wetting and solubilizing agents</td>
<td>Risk of serious adverse events, including death, when administered intravenously to neonates.</td>
</tr>
<tr>
<td>Propyl gallate</td>
<td>Antioxidant</td>
<td>Has shown a strong sensitizing potential in animals.</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Solvent</td>
<td>Use in large volumes in children is discouraged. Has been associated with CNS adverse effects, especially in neonates. Has to meet the standard of Ph.Int. to limit contamination with diethylene glycol.</td>
</tr>
<tr>
<td>Talc</td>
<td>Tablet glidant</td>
<td>Inhalation causes irritation and severe respiratory distress in children.</td>
</tr>
<tr>
<td>Thiomersal</td>
<td>Antimicrobial Preservative</td>
<td>Linked to toxicity in eye drops and vaccines. Should not be used in paediatric medicines.</td>
</tr>
</tbody>
</table>
5.3 Taste masking of oral liquids

The taste of a dissolved compound is to some extent associated with certain chemical structures. Amines, amides and other nitrogen-containing compounds like alkaloids frequently have a bitter taste, while certain imides like saccharin have a sweet taste. Alcohols, aldehydes and esters frequently have an aromatic character. A crude guide for taste masking is that an acidic taste is corrected by a sweetening agent, and that bitter taste is corrected by a sweetening agent and a flavour. The aim is to obtain a balance between the four basic sensations: acid, sweet, salty and bitter.

Paediatric patients are able to recognize sweetness and saltiness from an early stage and are also able to recognize sweet taste in oral liquids and estimate the degree of sweetness. Children seem to prefer higher levels of sweetness than adults. In paediatric medicine, therefore, the palatability of oral liquids is often improved by the use of sweetening agents and flavours; additional use of colouring agents (dyes) that “matches” the flavour should not be used unless necessary to cover drug-related unpleasant colour; see Section 5.3. The classical mean was to use syrup flavoured with a fruit aroma prepared from an extraction from fruits and hence coloured. Syrups contain a high concentration of sucrose, which generally should be avoided, in particular in preparations intended for long-term therapy because it promotes dental caries, and cannot be used in patients suffering from diabetes. Instead, sugar-free formulations should be preferred. Oral liquids containing a viscosity-increasing agent (e.g. hydroxypropylcellulose, agar) and a sweetening agent (e.g. sorbitol, sodium saccharin) are used to substitute syrups; the colloidal solution of the macromolecule has a coating effect in the buccal cavity thereby reducing a bitter taste.

Sweetening agents for oral liquids are sucrose, fructose, sorbitol, xylitol, glycerol and artificial sweeteners like sodium saccharin, ammonium and sodium glyceryrhizinate, and aspartame. Fructose like sucrose causes an elevation in blood glucose concentration and has, therefore, to be avoided in patients suffering from diabetes. Sorbitol and xylitol are not readily absorbed from the gut and are considered safe for diabetes patients. Sorbitol is, however, contraindicated in paediatric patients with hypoglycaemia and hereditary fructose intolerance because it is metabolized into fructose. Aspartame is 150-200 times sweeter than sucrose and may thus be harmful in patients with phenylketonurea.

High concentrations of intense sweeteners like sodium saccharine or aspartame may be unsuccessful in masking bitter taste in paediatric formulations; in high concentrations these agents appear to develop a bitter aftertaste. The intensity of sweetness at relative low concentrations may be enhanced by addition of sodium chloride.

Children’s preference for flavours may vary from country to country and seems to depend on social and cultural factors. Moreover, the proper choice of flavour is affected by the taste sensation by the API.

A review on successful taste masking of various APIs is given by Ernest et al. (J. Pharm. Pharmacol., 2007, 59:1043-1055).

Taste and smell of drug products can be evaluated using indirect analytical methods, by taste/smell sensors or qualitatively by taste panels. Information on methods to assess the taste of medicines is provided in the EMEA Reflection paper: Formulations of choice for the paediatric population.
5.4 **Colouring agents**


The number of colouring agents that are acceptable for use in medicines is limited because bodies like the US-FDA and the EU Commission have drawn up lists on permitted colouring agents. Permitted colouring agents include: (i) insoluble colours or pigments (iron oxides and hydroxides, titanium dioxide, calcium carbonate); (ii) soluble colours or dyes; and (iii) aluminium lakes consisting of a synthetic colouring agent precipitated on aluminium oxide; similar products based on silicium dioxide exist. Pigment colours and aluminium lakes are insoluble. Dyes used in pharmaceutical products include azo dyes (see Table 5.1), quinoline dyes (e.g. quinoline yellow) and some dyes of natural origin (e.g. carotenoids, anthocyanins, betanin).

The primary purpose of using colouring agents in tablets and capsules, usually by incorporating a pigment colour or an aluminium lake in the film coat, is to make similar products more distinctive, and to allow easier differentiation of a product to the patient on multiple medication. The use of insoluble colouring agents, when used in the coating or capsule shell, may contribute to opacity and thus aim towards the protection of light-sensitive drugs.

Colours for clear liquids are limited to dyes that are also widely used in foods and beverages. Concerns on the safety of dyes usually arise from reports on adverse effects following intake of food products. The use of azo dyes for paediatric medicines is discouraged. Possible more acceptable dyes are those of natural origin such as carotenoids and anthocyanins. However, the drawback with these colours is that they are unstable, their colouring power usually little, and that they show many incompatibilities.

6. **PHARMACEUTICAL DEVELOPMENT**

The goal of pharmaceutical development is to design a drug product and a manufacturing process that will consistently deliver the intended product performance and meet the needs of patients, healthcare professionals and regulatory authorities; in the present context the needs are associated with the paediatric population.

The approach to and extent of development can vary from company to company, and from product to product. As described in the *ICH Q8 guideline on pharmaceutical development* and its Annex, companies may choose either an empirical approach or a more systematic approach to product development. The contrast of these approaches is shown in Table 6.1 which is a copy of Appendix 1 to the ICH Q8 Annex. Table 6.1 does not detail the approaches. Current practices in the pharmaceutical industry vary and typically lie between these approaches.

In the context of a regulatory application, the section entitled Pharmaceutical Development is an integral part of the application for marketing authorization, for example via the WHO Prequalification Programme. It provides the applicant with an opportunity to present the knowledge that has been gained through the development work on a drug product and its manufacturing process. In general, the more information available to reviewers and inspectors, the greater will be their understanding of the product in question and the more flexible they can be in implementing regulation. Note, however, that it is the content of data, not the number of pages that provides a basis for the submission. A thorough literature search may provide some of
the information and commonly this part of a submission is a hybrid of new data and literature reports.

Table 6.1. Differing approaches to pharmaceutical development  
(From ICH Q8 Annex: Pharmaceutical Development)

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Minimal approach</th>
<th>Enhanced quality by design approach</th>
</tr>
</thead>
</table>
| Overall pharmaceutical development | ● Mainly empirical  
● Developmental research often conducted one variable at time | ● Systematic, relating mechanistic understanding of input material attributes and process parameters to drug product CQAs  
● Multivariate experiments to understand product and process  
● Establishment of design space  
● PAT tools used |
| Manufacturing process         | ● Fixed  
● Validation primarily based on initial full-scale batches  
● Focus on optimization and reproducibility | ● Adjustable within design space  
● Lifecycle approach to validation and, ideally, continuous process verification  
● Focus on control strategy and robustness  
● Use of statistical process control methods |
| Process controls              | ● In-process tests primarily for go/no go decisions  
● Off-line analysis | ● PAT tools used with appropriate feed forward and feedback controls  
● Process operations tracked and trended to support continual improvement efforts post-approval |
| Product specifications        | ● Primary means of control  
● Based on batch data available at time of registration | ● Part of the overall quality control strategy  
● Based on desired product performance with relevant supportive data |
| Control strategy              | ● Drug product quality controlled primarily by intermediate and end-product testing | ● Drug product quality ensured by risk-based control strategy for well understood product and process  
● Quality controls shifted upstream, with the possibility of real-time release or reduced end-product testing |
| Life-cycle management         | ● Reactive (i.e. problem solving and corrective action) | ● Preventive action  
● Continual improvement facilitated |
Pharmaceutical development should include, at a minimum, the following elements:

- A target product profile as it relates to quality, safety and efficacy
  - a prospective and dynamic summary of the quality characteristics to be achieved ideally. The target product profile forms the basis of design for the development of the product.
- Identification of the critical quality attributes of the drug product so that those product characteristics having an impact on product quality can be studied and controlled.
- Determination of the quality attributes of the API, excipients, etc. and selection of type and concentration of excipients to deliver drug product of the desired quality.
- Selection of an appropriate manufacturing process.
- Identification of a control strategy.

### 6.1 Design of dosage forms

The overall aims in the design dosage forms are:

- To achieve a homogeneous product so that each dose contains the intended amount of the API or APIs.
- To ensure an appropriate stability (chemical, physical and microbiological stability).
- To achieve that the time and rate of release is controlled and adapted to the chemical, physical and pharmacokinetic properties of the API.
- When necessary, that the formulation is adapted to the physiological conditions on the application site. This is in particular important for parenterals, eye drops and preparations for dermal application.

When tested, the dosage form must comply with the requirements for monographs on dosage forms and specific products in the Ph.Int. Consideration should be given to guidance provided in the general texts of Ph.Int., for example, the recommended limits for microbial contamination of dosage forms, that have to be met in the life-time of the product.

When requirements or guidance regarding an actual product are absent in the Ph.Int., other pharmacopoeias can be consulted, e.g. the specific monographs in the USP and British Pharmacopoeia (BP). Guidance on the efficacy of antimicrobial preservatives are provided in the JP, Ph.Eur. and USP. It is important, however, to note that the contents and efficacy requirements differ. In applying these criteria, consideration should be given to the fact that antimicrobial agents are basically toxic and that the concentration needed to meet, for example the Ph.Eur. criteria, may not be tolerated by the younger age groups. Concerns on some specific antimicrobial agents are given in Table 5.1.

Pharmacopoeias and regulators normally permit manufacturers to use alternative tests methods in their internal control of APIs, excipients and dosage forms. In the event of a dispute it is, however, the official test methods in the pharmacopoeia that must be used.

6.2 Dissolution testing

Dissolution rate is an essential performance characteristic of solid dosage forms including tablets and capsules of various types, suppositories, pessaries, implants and transdermal patches.

Methods for in vitro testing of the dissolution are provided in the Ph.Int. and in the major pharmacopoeias where some guidance on dissolution testing is also provided. Some publications that provide guidance on dissolution testing of finished dosage forms are listed in Table 6.2.

<table>
<thead>
<tr>
<th>Title/publisher/web site</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline on Submission of Documentation for Prequalification of Multisource FPPs: Supplement 1</td>
<td>2006</td>
</tr>
<tr>
<td>Dissolution Testing of Immediate Release Solid Oral Dosage Forms; FDA, CDER</td>
<td>1997</td>
</tr>
<tr>
<td>Guidance for Dissolution Testing of Solid Oral Dosage forms</td>
<td>1997</td>
</tr>
</tbody>
</table>

7. ORAL ADMINISTRATION

The oral route is the preferred route of administration to paediatric patients, and consequently many medicinal products should be available in both liquid and solid dosage forms. In both cases, administration of the accurate dose to the patient is important, and an acceptable taste is critical for compliance and concordance.

Solid dosage forms like capsules and tablets are generally convenient for caregivers and patients but their administration is limited to certain age groups, c.f. Table 3.1. The chemical and microbial stability is usually high while, depending on the formulation, physical stability problems, associated with, e.g. hardening of tablets affecting dissolution rate during storage, are not unusual. Their portability is improved compared to liquid formulations.

Most drug products are developed as solid oral dosage forms. It is known, however, that possibly 25% of adult patients have difficulty in swallowing (dysphagia) intact tablets and capsules; in the paediatric population the percentage is higher. Children over the age of 5 years can usually swallow a tablet or a divided tablet, and those as young as 3 years can be taught, particularly when they suffer from a chronic illness. Dysphagia challenges may be overcome by developing solid dosage forms to be dissolved, dispersed or mixed with food prior to administration, or dosage forms for chewing or administered to the mouth.

Paediatric patients who are acutely unwell may be frightened and less cooperative than usual, especially when they have fever or pain. Liquid dosage forms may be preferred to solid dosage forms or, if vomiting is a feature of the illness, rectal administration or injection can be necessary.

Paediatric patients with long-term illness who require continuing medication may be persuaded to take solid dosage forms, in particular when a liquid alternative is opposed.
7.1 **Biopharmaceutical parameters**

Development of dosage forms for oral administration must take into account the physiological conditions in the gastrointestinal system, in particular the pH-variation throughout the GI-tract, gastric emptying rate and the presence of digestive enzymes in the various segments.

There are important physiological and pharmacological differences between children and adults (Ernest et al. J.Pharm.Pharmacol., 2007, 59:1043-1055). In particular neonates are achlorhydric, i.e. their gastric pH is much higher than in adults. The gastric emptying rate is faster in neonates than in adults, while the gastric emptying rate in infants and children is slower than in adults. Furthermore, the clearance rate is greater in infants and children than in adults.

7.2 **Liquid oral dosage forms**

Liquid formulations include aqueous solutions, suspensions, emulsions and syrups, preferably of sugar-free type (c.f. Section 5.3). They are most appropriate for the younger age groups who are unable to swallow tablets and capsules, and they have the advantage of allowing variable dose volumes to be administered.

The dose volume is important for paediatric patients who accept a liquid oral preparation. Typical target dose volumes are not more than 5 ml for children under 5 years, and not more than 10 ml for children of 5 years and older. The more palatable the formulation, the higher the dose volume will be tolerated.

Since accurate dosing is important, a measuring device should always be provided with the multidose container. The volume actually measured with plastic spoons and similar devices is dependent on the physical characteristics, in particular the viscosity, of the liquid. It is, therefore, a part of the pharmaceutical development to ensure the dosing accuracy of the measuring device provided with the final dosage form. Use of a graduated pipette improves the flexibility of the dosing volume.

**Solutions**

In developing oral solutions for paediatric patients consideration should be given to minimize the dose volume to be administered. The aqueous solubility of the API is, therefore, important and may in many cases put a limit on the achievable concentration of the API.

General applicable means to increase the concentration of the dissolved API include:

- **pH adjustment.** Optimum pH for an oral solution is neutral to slightly acidic; alkaline reaction is associated with an unpleasant taste. pH values down to 3-4 is acceptable only when the solution lacks buffer capacity. Palatability of acid solutions can be improved by addition of sweetening agents.

- **Use of co-solvents.** Commonly used co-solvents with water in oral liquids, injections, etc. are ethanol, glycerol, propylene glycol and liquid macrogols (polyethylene glycols).

In oral paediatric solutions, the acceptable concentration of ethanol is relatively low (see Table 5.1). The risk for contamination of glycerol and propylene glycol with diethylene glycol can be avoided by applying the purity tests in the monographs of Ph.Int.

Use of the mentioned co-solvents in parenteral solutions is subject to limitations regarding their concentration because of undesirable effects like dehydration and irritation of tissues in high concentrations.
● Non-ionic surfactants, e.g. polysorbates, that may solubilize the API. Solubilization of lipid soluble vitamins with polysorbate in oral drops is a well-known principle. Polysorbates must not be used in IV injections to neonates c.f. Table 5.1.
● β-cyclodextrin may solubilize the API. It is considered safe in oral administration in contrast to parenteral administration.

Chemical instability of the aqueous solution of an API may in some cases, depending on the mechanism of degradation, be improved by pH-adjustment, eventually using buffering agents, addition of antioxidants or complexing agents. When sufficient stability cannot be obtained, solid preparations like powders or granules should be considered (see below).

**Oral drops**
Oral drops have traditionally been used to administer potent drugs in the form of small volumes dosed by dropping into a suitable liquid prior to intake. The use of a dropper or pipette offers great flexibility regarding the dose volume. Dosing of a few drops should generally be avoided because it is associated with uncertainty as to the dose volume. Dosing of volumes from ½ to a few millilitres by a pipette is recommended. During pharmaceutical development, the dosing device must be tested for its ability to deliver the intended volume.

Oral drops and also concentrates may be developed with a recommendation for dilution in beverage, e.g. fruit juice or milk, to improve palatability. Dilution volumes should be minimized to reduce risks of incomplete ingestion and under-dosage. It is important that manufacturers provide information on acceptable diluents to ensure satisfactory stability and to optimize taste.

**Suspensions**
Suspensions may be useful for formulation of APIs with poor taste characteristics because the amount of API in solution is minimized. An advantage of suspensions is that a higher load of the API is possible and, thus, the dose volume can be reduced. Examples of oral suspensions are formulations of antacids and gastrointestinal stabilizers that have low aqueous solubility.

Suspensions need physical stabilization so the intended dose of API can be taken from the container by volumetric means and administered. The ideal stabilizer shall have good wetting properties to the particulate solid and possess a high viscosity when the suspension is stored, and relatively low viscosity when the suspension is shaken. A variety of macromolecular compounds of both natural and synthetic origin are available. One of these is carageenan that should by avoided in paediatric medicines, c.f. Table 5.1.

**Powders and granules for reconstitution**
Formulation of solid preparations for reconstitution of oral liquids (solutions, suspensions, drops) is preferable when the liquid preparation has a low chemical stability and, hence, a too-short shelf-life. Examples of this type of formulation are phenoxyethylpenicillin and ampicillin that are stable against acidic gastric juice.

Powders and granules for reconstitution are usually provided in containers that can hold the reconstituted multidose liquid. The solvent should be provided together with the dry preparation, unless the solvent is water. In many cases, the solvent is formulated to render the reconstituted product stable and palatable.
For safety reasons, dry powder or granulation should be non-dusting, and it must be easily wetted and dissolved or dispersed when the solvent is added. For these reasons granules are preferred, alternatively lyophilized products. Hydrophilic binders and surfactants in granules can facilitate the reconstitution process.

The above comments on solutions, suspensions and drops apply to the reconstituted preparation.

7.3 **Solid oral dosage forms**

Solid oral dosage forms include a wide variety of dosage forms intended to be swallowed, chewed, dissolved or dispersed in suitable diluents, or applied to the mouth. Common to these are stability, accuracy of dosing and improved portability compared to liquid formulations. Formulation taste is usually not an issue because film- and sugar-coats can serve to improve palatability.

Since the API is present as a particulate solid, its aqueous solubility and dissolution behaviour are important for the release and absorption of the dissolved API (see Section 4.2).

Because many paediatric patients have problems in swallowing intact tablets, their size should be kept as small as possible. The shape of the tablet is also important; generally elongated, round tablets are preferred. Breaking of scored tablets (break-marks) may assist in that respect, but the use of scored tablets should be restricted to such formulations where the dosing accuracy of a halved tablet compared to the intact tablet does not have any implications on the clinical effect of the medication.

*Conventional tablets*

Conventional tablets are uncoated tablets, film- and sugar-coated tablets that 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. Furthermore, the coating may serve to stabilize the formulation by protecting it against humidity and other external factors.

Since this type of immediate-release formulation may be broken into parts or even crushed prior to administration to paediatric patients, it is important that the formulation chemist take this possibility into account.

*Effervescent dosage forms*

Effervescent oral dosage forms are tablets, granules and powders that are dissolved in water prior to administration. Effervescent dosage forms are alternatives to liquid dosage forms for APIs with insufficient stability in aqueous media. They are also more portable than liquid formulations.

The use of effervescent dosage forms usually requires a relatively large volume of water, the intake of which may be problematic to children. It is, therefore, helpful when the manufacturer indicates the minimum volume of water to be used for one dose.

To minimize the ingestion of bicarbonate, children should be instructed not to drink the solution before effervescence has subsided.

Effervescent dosage forms are not suitable for patients having renal insufficiency because of the high content of potassium or sodium.
Dispersible tablets

Dispersible tablets are intended for use in the same way as effervescent tablets. The advantage of dispersible tablets compared to effervescent tablets is that the problems with bicarbonate, sodium and potassium are avoided.

Chewable tablets

Chewable tablets are non-disintegrating tablets intended to be chewed and swallowed. This is a valuable paediatric dosage form for children of 2 years and older. Administration to younger age groups should be supervised to ensure thorough chewing. Among the types of products available as chewable tablets are antacids, antibiotics, analgesics, anti-asthmatics and vitamins.

Chewable tablets should have a smooth, rapid disintegration. They must possess good organoleptic properties, including a good “mouth-feel” which is influenced by the solubility, particle size and shape of the API. They are usually formulated with a high content of water-soluble sweetener like mannitol that provides a sweet, cooling taste and mouth-feel. The sweetening agent may be supplemented with a flavouring agent. Other sweetening agents, in particular those suited to direct compression, are used in chewable tablets, e.g. sorbitol and xylitol.

Although chewable tablets must be hard and of good mechanical resistance, it is important for the paediatric patient that they are easy to break by chewing.

Powders and granules

For APIs that are unstable or cannot be taste-masked in liquid preparations, powders and granules offer a suitable alternative. Formulations are offered in multidose containers provided with a measuring device, or in the form of single-dose sachets. They may also be supplied in the form of capsules, the content of which can be sprinkled onto food.

Doses of powders and granules may be taken directly in the mouth or, even better, by mixing the prescribed dose with a small amount of food, or with a drink prior to administration. The product information should specify which commonly available foods are suitable for mixing and eventually list those foods to be avoided due to stability, compatibility or taste issues. Granules are prepared by wet-granulation using a hydrophilic binder such as povidone, that promotes wetting and dissolution of the API.

Orodispersible dosage forms

Orodispersible dosage forms are orodispersible tablets, oral lyophilisates and thin films to be placed on the tongue where they disperse rapidly or “melt” by dissolution in the saliva, whereafter the dissolved dose is swallowed. They are easy to administer, do not require additional water and are difficult to spit out, so dissolution is rapid. They, therefore, hold great promise especially for younger children and may provide a range of dosages appropriate for paediatric patients.

8. RECTAL ADMINISTRATION

Rectal administration is used to achieve either local (e.g. laxative, anti-inflammatory) or systemic effects. The rectal route is an alternative to the oral route when the API is rapidly degraded in the GI-tract or shows significant first-pass metabolism. It may be possible to obtain
an immediate systemic effect by rectal administration, e.g. administration of a rectal solution containing diazepam.

Rectal dosage forms, in particular suppositories and rectal liquids or enemas, are suitable for most age groups, c.f. Table 3.1, when administration via the oral route is contraindicated, for example due to vomiting, difficulty in swallowing, unconsciousness, asthma symptoms, refusal to eat (sitophobia), anorexia, etc., or the oral route is rejected because of palatability issues.

When administering rectal preparations to paediatric patients, there is a risk of the dosage form being expelled prematurely, in particular when the dose has an irritating effect. Concordance and compliance of rectal preparations may be lower than for oral dosage forms, as the rectal route is poorly accepted by caregivers and patients in some regions and cultures. It is for this same reason that the acceptability of suppositories and enemas is relatively low among children of school age, c.f. Table 3.1.

Suppositories

Suppositories for use in the paediatric population must be adapted to the age of the patient with regard to both size and strength. Typically, suppositories for infants weigh approximately 1 g, half the weight of the adult suppository. Since many suppositories contain the API as solid particles that may be unevenly distributed in the individual dose, suppositories should not be cut e.g. in half, in an attempt to adapt the size to the age of the child; they have usually already been formulated in various strengths for various age groups.

Two types of suppository bases are available: (i) those that are insoluble in water, e.g. hard fat; and (ii) those that are soluble or miscible with water, e.g. macrogols. Insoluble bases must melt below body temperature (\(< 36^\circ C\)) to allow release of the API to the rectal liquid. The soluble bases have to be dissolved in or mixed with the rectal fluid which usually amounts to 1-3 millilitres only. Bases like macrogols (polyethylene glycols) are, however, strongly hydroscopic and attract additional water from the rectal mucosa. Although this effect may be reduced by moistening with water prior to insertion, this type of suppository may have an irritating effect upon the child. Hard-fat suppository bases are non-irritant but animal studies have indicated that bases with a high hydroxyl value may be irritant.

Rectal liquids (enemas)

Rectal liquids are solutions, suspensions or emulsions based on water or vegetable oil. The volume of liquid to be administered must be adapted to the intended action (local or systemic) and to the age of the child. For systemic therapy, the volume should be as small as possible to achieve accurate delivery, good absorption and absence of irritation. Volumes of 1-5 millilitres may be acceptable. The delivering device should allow simple delivery; the rectal tube should be of a length appropriate to the age of the child, and should not cause injury. The use of pre-filled syringes equipped with a rectal tip facilitates individual dosing and may reduce the need for several strengths or dosages.

Formulation of aqueous rectal liquids has the same feature as the formulation of other liquids. They may contain viscosity enhancing agents, pH-adjusting substances, surfactant and antimicrobial agents. Non-ionic surfactants are preferable because ionic surfactants are frequently irritating to the rectal mucosa.

Rectal liquids may be prepared by dissolving a powder or a tablet in water immediately before administration.
Other dosage forms

Other dosage forms intended for rectal administration include rectal capsules, semi-solid preparations and foams. Ointments, creams, gels and foams are intended to achieve a local effect. They are provided in containers equipped with a rectal tip or an applicator to facilitate administration.

9. INJECTABLES

Parenterals are administered by intravenous (IV), intramuscular (IM), subcutaneous (SC) and intradermal administration. IV administration of aqueous liquids is the preferred route of administration to paediatric patients and is applicable to all age groups, c.f. Table 3.1. SC administration is applicable especially to the lower age groups, while IM administration, because of the pain associated with an intramuscular injection, is limited to the oldest age groups.

Aqueous parenterals must be adapted to the physiological conditions on the application site. This means that, in addition to sterility, they should have as far as possible a pH of approximately 7.4 and an osmolality corresponding to a 0.9% NaCl solution. The tolerances for deviating pH and osmolality are dependent on the route of administration, the volume to be injected and whether the preparation has a buffering capacity. A small volume of an aqueous liquid injected intravenously is rapidly diluted in the bloodstream, allowing tolerable pH variations from approximately 3 to 9, even when there is some buffer capacity. SC administration is much more sensitive for deviations, simply because the dilution of the injected volume and its escape from the application site proceeds slowly.

When pH adjustment is required for stability reasons, solutions of strong acids (HCl) and bases (NaOH) should be used because buffering effects are minimized.

In the formulation of parenterals careful consideration must be paid to the concentration and nature of excipients and risk of adverse effects when they are introduced into the body. This is valid in particular for antimicrobial agents and surfactants. Most surfactants of ionic and non-ionic nature cannot be used because of adverse effects like haemolyses; examples of suitable surfactants are Pluronics, Cremophor and lecithin.

The use of co-solvents to achieve a sufficient concentration of the API includes the co-solvents mentioned in Section 4.2. Propylene glycol should not be used in excess of approximately 20% because higher concentrations cause pain. The same is valid for the liquid macrogols in concentrations above approximately 30%.

Intravenous injections

Only aqueous solutions can be injected intravenously. Emulsions intended for IV administration are marketed; the dispersed oily phase consists of very small droplets that can pass even the narrowest capillaries. Formulation and manufacture of such emulsions is very delicate and technically demanding.

Many APIs are presented as powders or lyophilisates to be reconstituted before administration. It is important that the manufacturer provides detailed instructions regarding the reconstitution and stability (storage conditions and time) of the reconstituted solution. The characteristics of the reconstituted liquid shall comply with the requirements for parenterals in the Ph.Int.
The solution to be administered should as far as possible be isohydric and isoosmotic but deviations can be tolerated dependent on the volume to be injected; for larger volumes (parenteral infusions), deviations are not acceptable unless they are intended to be co-infused with other liquids.

Paediatric injections may be produced in a variety of sizes and strengths to adapt to the age and weight of the paediatric patient. It is helpful to specify the size of syringe that permits accurate administration.

**Intramuscular injection**

Intramuscular injections are generally painful for children so the intravenous route is preferable, especially when several regular injections are required. Intramuscular injection may easily be accompanied by several complications related to damage following inappropriate site of needle insertion, needle size and angle of injection. Injection volumes for IM administration must be small and should not exceed 1 ml at a single site. The tolerance for nonphysiological pH and osmolarity is less than that for IV administration.

**Subcutaneous administration**

The site of injection and injection volumes are important. The injection volume should not exceed 1 ml for older children.

If a nonphysiological pH must be used for stability reasons, it is important that the preparation has the lowest possible buffer strength. Buffers containing citrates cause local pain.

**Intradermal administration**

The intradermal route is used for diagnostic agents and some vaccines. The technique for accurate intradermal injection is difficult, especially for neonates, infants and toddlers.

10. **REFERENCES**


7. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on*


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