European Medicines Agency
*Pre-authorisation Evaluation of Medicines for Human Use*

London, 28 July 2006
EMEA/CHMP/PEG/194810/2005

# COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

# REFLECTION PAPER: FORMULATIONS OF CHOICE FOR THE PAEDIATRIC POPULATION

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| **AGREED BY PAEDIATRIC WORKING PARTY & QUALITY WORKING PARTY** | May 2005 |
| **ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION** | 23 June 2005 |
| **END OF CONSULTATION (DEADLINE FOR COMMENTS)** | 31 December 2005 |
| **AGREED BY PAEDIATRIC WORKING PARTY** | 28 July 2006 |
| **ADOPTION BY CHMP** | 21 September 2006 |

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## BACKGROUND AND OBJECTIVE

- The development of paediatric formulations, particularly those suitable for very young children, can be challenging to the pharmaceutical scientist. There is only limited knowledge available on the acceptability of different dosage forms, administration volumes, dosage form size, taste, and importantly, the acceptability and safety of formulation excipients in relation to the age and development status of the child.

- Many medicinal products are not currently available in formulations suitable for administration to the paediatric population. Consequently, healthcare professionals frequently resort to the preparation and administration of unlicensed formulations by manipulation of adult dosage forms.

- The draft European Regulation on medicinal products for paediatric use (released by the European Commission on 29th September 2004) requires that the paediatric investigation plan describes any measures to adapt the formulation of the medicinal product as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.

- The aim of this document is to assist in the development of paediatric formulations which enable neonates, infants and children of all ages, and their caregivers, to have access to:

  – A range of authorised dosage forms permitting safe, accurate dose administration, which enhances compliance and concordance with minimum impact on lifestyle, and reduces the risk of medication errors.

  – Formulations containing only excipients known to be safe and effective for the age of the paediatric patient.

  – Dosage forms safely and effectively adapted to the needs of paediatric patients.if appropriate commercial dosage forms are not available.

- Consequently this document has been written to summarise available information on paediatric formulations, and to use examples of authorised paediatric products to guide all parties involved in the development and manufacture of medicinal products in improving the availability of suitable paediatric formulations. It is not intended as a regulatory guidance document which defines requirements to be fulfilled.

This document should be read in conjunction with relevant existing CHMP guidance documents, for example the guideline on Pharmacokinetics in children and relevant ICH guidelines such as E11, Clinical Investigation of Medicinal Products in the Paediatric Population (CHMP/ICH/2711/99).

# 1. NEONATES, INFANTS AND CHILDREN

## 1.1 Introduction

Infancy and childhood is a period of rapid growth and development. The various organs, body systems and enzymes that are exposed to active substances and excipients, generally develop gradually but at different rates. Dosage varies throughout infancy and childhood, in later childhood most closely following changes in body surface area and weight, such that doses are frequently quoted as amount/$m^2$ or amount/kg. Doses may be expressed for different age groups. Pharmacokinetics, pharmacodynamic response to substances, and adverse reactions, may also vary with age.

Neonates, infants and children gradually develop their cognitive and motor skills including co-ordination. Their dependence on parent or caregiver for feeding is also relevant to their ability to tolerate or administer different pharmaceutical dosage forms. Some paediatric patients with disabilities will lag behind their age group. The age at which children can be responsible for administration of their own medicinal products will vary greatly. In older children and adolescents life style and peer pressures may affect compliance.

The magnitude of doses required through childhood can vary 100 fold and the ability to cope with different dosage forms can also vary considerably. Thus, if a medicinal product is to be used in all age groups, a range of different dosage forms should be available providing different strengths or concentrations to allow simple, accurate and safe dosing.

## 1.2 Age definitions

The guideline on clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99) uses the following age groups in relation to developmental stages.

- Preterm newborn infants
- Term newborn infants (0-27 days)
- Infants and toddlers (1 month to 23 months)
- Children (2 – 11 years)
- Adolescents (12 – 16 or 18 years)

These age ranges reflect biological changes – the changes after birth; the early growth spurt; gradual growth from 2-12 years; the pubertal and adolescent growth spurt and development towards adult maturity. The age group 2-11 years could be further subdivided in terms of the child's ability to accept and use different dosage forms, e.g. into pre-school children (2-5 years) and school children (6-11 years), as described in table 3.1.
The increasing survival of very preterm newborns of 23-24 weeks gestation with extremely low birth weight <1000g presents special pharmaceutical challenges within the 'preterm' category relating mainly to size of dose.

## 1.3 INFLUENCES ON THE ADMINISTRATION OF MEDICINAL PRODUCTS

### 1.3.1 Capability

The ability to use different dosage forms varies greatly. This will relate principally to age, physical development and ability to co-ordinate, but also to psychological development and understanding. The ability to effectively use different inhaler devices illustrates this well with a gradual progression from holding a chamber with mask, spacer, breath-activated device and metered dose inhaler from infant to adolescent. A major concern is at what age children can safely swallow solid oral dosage forms such as tablets or capsules. Again this is generally a factor of age and health status but there are significant inter-patient differences around an average of about 6 years. Taste, smell and texture will be important

factors for any medicine administered orally; additionally, rate of dissolution and the ability to keep medication at the site of absorption will be important for buccal or sublingual administration. Children are unlikely to tolerate repeated administration of medicinal products, which are uncomfortable, painful or stressful.

### 1.3.2 Influence of illness

*Acute*

Paediatric patients who are acutely unwell may be frightened and less co-operative than usual, especially if they have fever or pain. Liquid medicinal products may be preferred since the struggling child may choke on a solid dose form but liquids may be spat out and lost. Vomiting may also be a feature of the illness making rectal administration or injection necessary.

*Long term*

Paediatric patients with long-term illness requiring continuing medication may be persuaded and trained to take solid dosage forms from a relatively early age of 3-5 years. This is particularly true if taste is a problem with liquid alternatives. Regular injections may be tolerated but distraction techniques appropriate to age and other methods of reducing pain may be required.
It is preferable to offer a range of dosage forms so that paediatric patients and caregivers have choice since compliance over a long period may then be enhanced.

### 1.3.3 Parent/caregiver convenience

Parents or adult caregivers are responsible for administering medicinal products to many paediatric patients. Whilst preference of the child for a particular dosage form is important, attention should also be given to the ease of administration by the parent or caregiver. Administration of rectal medicinal products may not be popular and can be difficult in some emergency situations.

### 1.3.4 Childcare and school

Many pre-school children attend nurseries or childcare facilities in which they are looked after by caregivers who are not their parents. School-age children are usually under the care of a teacher or teaching assistant but a nurse may be attached to the school. Longer-acting preparations may obviate the need for administration during school hours. However, there is increasing acceptance of the need to administer medicinal products to children during the school day if longer-acting preparations are not appropriate. The administration of medicinal products in a school environment can be facilitated by a relevant and appropriate pharmaceutical form or delivery system.

### 1.3.5 Adolescence

Information on handling medicinal products during puberty is scarce.

Adolescents may be rebellious and reject medicinal products they have previously taken.

They are developing independence from adults and will usually be responsible for their own medicinal products administration.

Life style changes mean that discrete, portable dosage forms become increasingly important.

### 1.3.6 Disability

Some paediatric patients have severe physical and/or mental disability and are unable to administer their own medicinal products. They may require feeding tubes so that enteral medicinal products must be liquids or preparations that can be manipulated to allow them to pass through small bore tubes. Interactions with enteral feeds and administration apparatus are important.

These paediatric patients may not obviously express pain or discomfort and may be unable to describe side effects of medicinal products or their preferences.

### 1.3.7 Cultural differences

There may be differences in the acceptability of different routes of administration in the different countries of Europe as well as by different religions. For example, the rectal route of administration is not generally favoured in the UK.
Cultural differences may also arise with regard to taste.

## 1.4 DEVELOPMENTAL PHARMACOLOGY

A knowledge of the changes to drug handling which occur during infancy and childhood assist in understanding the differences in dose and dose frequency as well as differences in bioavailability. Each is of importance in determining the best dosage form for different age groups. A brief summary follows but readers are referred to the bibliography for more detailed information.

### 1.4.1 Absorption

Developmental changes, for example, in the gastrointestinal tract and skin can significantly alter the rate and extent of bioavailability.

*Oral*

Gastric pH is relatively high in the neonatal period; gastric emptying increases; gut motility matures during early infancy and there are changes to splanchnic blood flow, intestinal drug-metabolising enzymes, micro flora and transporters. There are few published bioavailability studies but in general, rate of absorption is slower in neonates and infants than in older paediatric patients.

*Buccal*

There is little information on developmental changes in the buccal mucosa but there may be a higher permeability of the mucosa in paediatric patients compared to adults (1).

*Intramuscular*

There is little information on absorption of substances administered by the intramuscular route in infants and children. There is evidence of reduced muscle blood flow and contractions in neonates but absorption may be increased by the rich supply of capillaries so that intramuscular absorption may be greater in infants than older paediatric patients.

*Topical*

Infants and young children have a larger surface area to weight ratio than adults. Substances absorbed through the skin have potential to reach higher blood and tissue levels and may result in toxicity (for example, adrenal suppression with topical corticosteroids). The stratum corneum is thin in neonates and throughout childhood the epidermis is perfused and hydrated to a greater extent than in adults. Percutaneous absorption may be increased and systemic effects enhanced through the high body surface area to weight ratio.

*Rectal*

Retention of suppositories may be an issue for young paediatric patients. Bioavailability of some substances may be variable.

*Pulmonary*

Deposition and absorption through the lung mucosa may be a useful, non-invasive route of administration for systemic effect; drugs intended for local effect may be absorbed and produce systemic adverse effects.

*Nasal*

Significant absorption of active drugs intended for local effect may lead to systemic adverse effects but absorption through the nasal mucosa may also provide a useful route of administration. Some paediatric patients will prefer intranasal administration to injection. Irritation of the mucosa by the formulation may be painful or produce a 'runny nose'. Nasal mucosal congestion and secretions may influence absorption.

### 1.4.2 Distribution

There are age-related changes in body composition, protein binding and active transport mechanisms. The blood-brain barrier is considered to be immature in infancy but there is little information on its maturation.

*Body water/fat*

The proportion of body water per kg of body weight is high in the first weeks of life and gradually declines whilst proportion of body fat is low (especially in pre-term neonates) and increases until maximum proportion is reached at about 1 year of age. A greater proportion of body water is extra-cellular in young infants. Thus, water soluble substances (e.g. aminoglycosides) will have a higher volume of distribution in the very young whilst fat soluble substances (e.g. diazepam) may be expected to have their greatest volume of distribution in older infants and toddlers.

*Protein binding*

The amount and composition of drug-binding proteins gradually changes during infancy with protein binding generally reduced in neonates and infants so that a greater proportion of highly protein-bound drugs are free and active in plasma. During the neonatal period competing substances such as bilirubin and free fatty acids may also influence or be affected by drug-protein binding.

### 1.4.3 Metabolism

The major site of drug metabolism is the liver involving phase 1 reactions such as oxidation and reduction and phase 2 reactions such as conjugation with glucuronic acid and sulphation. Metabolism converts fat-soluble compounds into those with greater water solubility for elimination in the urine or bile. In general, clearance of substances metabolised in the liver is greater in children than in adults, requiring higher doses per kg body weight.

The main pathway for phase 1 reactions is oxidation using the cytochrome P450 dependent (CYP) enzymes and these enzymes are generally immature at birth reaching maximum values at about 2 years of age. Hepatic clearance of some substances will be greater on a per kg body weight basis than for adults e.g. carbamazepine, theophylline. The different CYP families of enzymes mature at different rates and there may be significant inter-individual variation.

Phase 2 reactions include glucuronidation and sulphation. Many different enzymes are involved and they develop at different rates such that metabolism of substances may vary considerably in infancy both qualitatively and quantitatively. Neonates are unable to conjugate benzoic acid efficiently and this is of great importance to the use of benzyl alcohol as an excipient in this age group since its metabolite benzoic acid can accumulate and is toxic.

The ontogeny and pharmacogenomics of metabolising enzymes for active drugs is receiving increasing attention but there is little information about the effect on excipients.

#### 1.4.4 Renal elimination

Water-soluble substances and metabolites may be eliminated from the body by glomerular filtration e.g. gentamicin, or by tubular secretion e.g. penicillins. Neither process is mature at birth and development to adult capacity may take 6-12 months.

### 1.5 CONCLUSION

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 will be preferred. The following will be important considerations:

- Minimal dosage frequency
- One dosage form fits all or a full range
- Minimal impact on life style
- Minimum, non-toxic excipients
- Convenient, easy, reliable administration
- Easily produced, elegant, stable
- Cost and commercial viability

## 2. ROUTES OF ADMINISTRATION

### 2.1 Oral administration

The oral route of administration is commonly used for dosing medicinal products to paediatric patients and consequently many medicinal products should be available in both liquid and solid oral dosage forms. The variety of different oral dosage forms available, such as: solutions, syrups, suspensions, powders, granules, effervescent tablets, orodispersible tablets, chewable tablets and gums, mini tablets, innovative granules, conventional immediate release and modified release tablets and capsules, make this route extremely useful for the administration of medicinal products to paediatric patients of a wide age range (see Section 3).

This section reviews the different types of oral dosage forms that are available for paediatric use and focuses on key factors to improve their quality and acceptability for the paediatric population. For all oral dosage forms, an acceptable taste is critical for compliance and concordance. The importance of taste evaluation during the development of paediatric oral formulations is discussed in more detail in Annex 2.

#### 2.1.1. Liquid formulations

Liquid formulations include solutions, syrups, suspensions and emulsions and are most appropriate for younger paediatric patients (e.g. birth to 8 years) who are unable to swallow capsules or tablets.

The dose volume is a major consideration for the acceptability of a liquid formulation. Typical target dose volumes for paediatric liquid formulations are $\leq$ 5 ml for children under 5 years and $\leq$ 10 ml for

children of 5 years and older. However, the more palatable the formulation, the higher the dose volume which will be tolerated. Large volume doses may be inconvenient for both patient and carer.

Oral solutions of very small dose volumes (e.g. oral drops and concentrates) may be developed, with recommendation for dilution in a beverage, often fruit juice or milk, to improve palatability.

It is important that manufacturers provide information on acceptable diluents to ensure satisfactory stability and optimise taste. Also, dilution volumes should be minimised to reduce the risk of incomplete ingestion and under-dosage.

Suspensions may be very useful for formulation of substances with poor taste characteristics; as by minimising the amount of drug in solution, the palatability of the formulation can be improved. Also, suspensions can facilitate higher drug loading than solutions and hence can reduce the dose volume. Suspensions containing coated pellets, or ion exchange resins may be useful to modify drug release. However if taste and drug release characteristics are appropriate, solutions are preferred over suspensions due to better oral acceptance. In addition, it is necessary for suspensions that sufficient information on the need to shake the product to ensure correct dosing is provided.

### 2.1.2. Oral Effervescent Dosage Forms

Oral effervescent dosage forms include tablets, granules and powders that are dissolved in water prior to administration. Effervescent products are alternatives to liquid dosage forms for substances with insufficient stability in aqueous media. They are also more portable than conventional liquid formulations.

The following points should be considered when formulating effervescent dosage forms:

- Effervescent products should always be fully dissolved prior to administration, and large volumes of diluent may be required to do so which can be problematic for children. Therefore, it may be helpful to indicate the minimum volume an effervescent product can be dissolved/dispersed in as well as the solubility of the drug so that fractional doses can be given, if necessary.
- To minimise the possibility of ingesting bicarbonate, children should be instructed not to drink the solution until the effervescence has subsided.
- As effervescent tablets normally contain high sodium and/or potassium ion concentrations, they may not be suitable for all patients, e.g. those with renal insufficiency.

### 2.1.3. Oral Powders and Multiparticulate Systems

For substances that are not stable or cannot be taste masked in liquid preparations, powders or multiparticulate formulations (e.g. beads, granules and mini tablets) are encouraged. These can be dosed directly into the mouth of the paediatric patient, or by mixing the prescribed dose with a small amount of soft food or with a drink prior to administration. Formulations can be provided in a bottle with dosing scoop, or in single-dose sachets. They may also be supplied in the form of capsules the contents of which can be sprinkled onto food.

The product information should specify which commonly available foods are suitable for mixing with the preparation, and also list foods that should be avoided due to stability, compatibility or taste issues.

### 2.1.4. Orodispersible dosage forms

Orodispersible dosage forms may comprise orodispersible tablets, lyophilised wafers and thin films and are placed in the mouth where they disperse or “melt” on the tongue. Orodispersible dosage forms hold great promise for children as they are easy to administer, do not require additional water and, as long as dispersion is rapid, are difficult to spit out and could provide a range of dosages appropriate for use in younger children.

Only a few products are currently authorised for use in the paediatric population and only above the age of six years.
Different orodispersible dosage forms will differ in their dispersion time, mouth feel, potential for taste masking and in the dose, which can be formulated. Taste will be a particular challenge as there will be a limited quantity of sweeteners and flavours that may be incorporated into this dosage form. The use of insoluble salt forms and/or taste masking technologies, such as particle coating, may be considered to improve palatability. It should be noted that while these strategies reduce dissolution in the mouth and hence taste perception, they might affect the pharmacokinetic profile.

### 2.1.5 Chewable tablets

Chewable tablets are a valuable paediatric dosage form for children of 2 years and older. They are considered to be safe in younger age groups if administration is supervised to ensure thorough chewing to reduce the risk of inhalation or ingestion of tablet fragments (1).

Chewable tablets should have a smooth, rapid disintegration. Ideally, the formulation should contain non-cariogenic sweeteners. Among the types of products available as chewable tablets are antacids, antibiotics, anticonvulsants, analgesics, anti-asthmatics, vitamins and cold/allergy preparations (2, 3)

### 2.1.6 Chewing gum

Medical chewing gum has only been used for relatively few paediatric formulations such as dimenhydrinate and fluoride. However, it may be a suitable dosage form for children as most children of age 6 years or older are familiar with chewing gum. Chewing gum is easy to administer, does not require additional water and may be taken anywhere.

It may be possible to mask the unpleasant taste of active substances by sweeteners and flavours added to the chewing gum. The release of the active substances is controlled by various means such as solubilisers, ion exchange, encapsulation and the amount of gum base. The minimum chewing time needed to ensure complete release of the required dose should be determined.

However, as chewing gum is also appreciated by children as a confectionary, care needs to be taken to restrict their access to any medical chewing gum.

### 2.1.7. Tablets and capsules

Solid oral dosage forms such as tablets and capsules can offer advantages of greater stability, accuracy of dosing and improved portability over liquid formulations. Formulation taste is rarely an issue, with film and/or sugar coats used to improve palatability. The primary limitation for paediatric use is that solid oral dosage forms can present significant problems for young children and adolescents who have difficulty swallowing. The age at which children can swallow intact tablets or capsules is highly dependent on the individual and the training and support that they receive from healthcare professionals and caregivers. Anecdotal evidence suggest that with support and training, children aged < 6 years can learn to take solid dosage forms, particularly for chronic therapy and/or when faced with unpalatable liquid formulations as an alternative. The size of tablets and capsules should be kept as small as possible. Dosing of multiple mini-tablets may be preferred over a single, larger dosage form and can allow dosing flexibility. Scoring of tablets to allow accurate breakage into halves or quarters should also be considered.

One of the key advantages of solid dosage forms is that they do offer the opportunity for the development of modified-release formulations, which is technically more challenging for liquid formulations. The availability of paediatric modified-release dosage forms is discussed in more detail in Section 6.

## 2.2 Buccal and Sublingual Routes

### 2.2.1 Advantages and Disadvantages of Buccal/Sublingual Administration

The oral trans-mucosal route offers some advantages over the peroral route. Taste is one of the major determinants of mucosal contact time and of particular importance for products especially designed for children. Fundamental limitations associated with this mode of administration are the lack of co-operation of children, their difficulties in co-ordination, and the risk of choking and aspiration. The accuracy of dosing is also a key problem, since oro-mucosal dosage forms may be swallowed or spat out prior to sufficient absorption taking place.

### 2.2.2 Oro-mucosal Dosage Forms and Formulation Considerations

The applicability of oro-mucosal dosage forms in the treatment of paediatric patients needs to be evaluated for safety and compliance issues, and generally depends on the age of the child.

- Buccal or Sublingual Tablets: Buccal tablets are designed to disperse slowly to give a prolonged release effect, whereas those for sublingual use dissolve promptly and provide a rapid pharmacodynamic response. Limitations include the restricted number of successful drug candidates, the restrictive size of the buccal pouch and sublingual area, and concern over palatability and local irritation (1). For reasons of safety and uncertainty about co-operation, this type of product is not suitable for young children.

- Muco-adhesive Preparations are intended to be retained in the oral cavity by adhesion to the mucosal epithelium and may modify systemic drug absorption at the site of application. They may be supplied as muco-adhesive buccal tablets or other solid and semi-solid preparations. These forms might even be suitable for younger children but further evaluation is required.

- Lozenges are hard solid dosage forms intended to dissolve or disintegrate in the oral cavity. They are usually designed to administer active substances locally to the mouth and pharynx, but can also contain substances for systemic absorption. They are only likely to be an acceptable dosage form for older children.

- Chewing Gum releases the active substance to saliva during chewing and may be used for both local and systemic treatment. Chewing gum should be chewed for a certain period of time (usually 10 – 20 minutes) to ensure release of the intended dose and afterwards the gum residue should be expelled. This dosage form is likely to be acceptable for children of 6 years or older.

- Liquid Preparations (e.g. oro-mucosal drops, sprays) are solutions, emulsions or suspensions intended for local or systemic effect. They are applied by instillation, spraying or squirting (oral syringe) into the oral cavity or onto a specific part of the oral cavity. The applicability needs to be assessed on a case-by-case basis.

## 2.3 NASAL ADMINISTRATION

### 2.3.1 Advantages and Disadvantages of Nasal Administration

Many medicinal products introduced into the nasal passage are intended for localised effects on the mucous membrane and underlying tissues. Examples are topical decongestants or anti-inflammatory medicinal products used to treat a rhinitis or allergy-related indications. However, the nasal route provides direct access to the systemic circulation, and may be an attractive (needle-free) alternative to invasive administrations.

Nasal administration may lead to unwanted systemic effect, may irritate the mucosa or cause pain and be ineffective if secretions are abundant.

### 2.3.2 Nasal Dosage Forms and Formulation Considerations

The development of locally acting nasal products has to focus on a minimum of drug absorption into the nasal mucosa and a maximum residence time. In contrast to that, systemically acting products require an efficient absorption into the bloodstream. Nasal preparations are liquid, semi-solid or solid preparations intended for administration to the nasal cavities to obtain a systemic or local effect:

- Nasal Drops are intended for instillation into the nasal cavity and usually are supplied in multidose containers with a suitable dosing device. On account of insufficient reliability in dosing characteristics, nasal drops are not recommended for administering highly potent (systemically acting) drugs. From an anatomical point of view, nasal drops may be preferred for infants, since their nasal cavity is so small that one or two drops can cover the whole mucosa (1).

- Nasal Sprays are applied to the nasal cavity for local and/or systemic effects. They can be supplied in squeeze bottles, mechanical-dispensing systems or pressurised containers (nasal aerosols). The applicability of the traditional squeeze bottle is restricted due to its significant dose variability. In contrast to that, pressurised metered dose systems for nasal administration (nasal aerosols) are very reproducible in dosing and droplet size distribution. A major disadvantage is the puff's strong impact on the nasal mucosa, which results in local irritation (coldness) and additionally restricts the area for drug deposition. Mechanical dispensing systems, which basically consist of a pump with metering chamber and actuator, are available in great variety and can thus be chosen depending on the technological requirements (e.g. two-chamber systems for unstable formulations) and the needs of the patient target group. Actuators for paediatric application are slimmer in their geometry and the dosage volume is reduced (1). Acceptability and compliance for young children requires further evaluation.

- Nasal Powders are dispensed by means of a suitable delivery system. Powder dispensing systems are preferably used for drug substances, which are more stable in a dry and solid state (e.g. peptides and vaccines). They can be divided into passive and active delivery systems. Active systems are fitted with a mechanism that allows pressure to be built up and eject the powder into the nostril. These systems are especially suitable for children (1).

A variety of drug substances are being evaluated for transnasal delivery to the systemic circulation. Nasal sulfentanil, midazolam and S-ketamine have been used for pre-induction of anaesthesia in paediatric patients (2, 3). The nasal route is also receiving attention for the management of postoperative pain (patient-controlled-intranasal analgesia) and with diamorphine for pain relief following trauma. Moreover, the nasal administration of peptides (e.g. desmopressin) and vaccines is an attractive route in terms of efficacy and patient acceptance (1, 4).
During product development, the drug properties, the reproducibility and performance characteristics of the device, and the nasal anatomy and physiology of the paediatric target group have to be considered. In order to enable the required deposition pattern in the nasal cavity, the delivery system has to be adapted in dose volume and dimensions of the nasal actuator. The formulation needs to be as far as possible non-irritating, without adversely affecting the functions of the nasal mucosa and its cilia (5). Penetration enhancers should be shown to be safe and effective in the target population.

## 2.4 RECTAL ADMINISTRATION

### 2.4.1 Introduction

The rectal route of administration can be used to achieve either local (e.g. laxative, anti-inflammatory) or systemic (e.g. antipyretic, analgesic, anti-nauseant, anticonvulsive, sedative) effects.

In paediatric, as in adult therapy, rectal dosage forms may be indicated for a number of reasons:

- The patient cannot take medications orally or the oral route is contraindicated, for example due to nausea and vomiting, obstructions of the upper gastrointestinal tract, continuous nasogastric

suctioning or unconsciousness. Typical medication examples include paracetamol, diclofenac, carbamazepine and domperidone suppositories.
- Immediate systemic effects are required, for example to manage repetitive epileptic seizures (e.g. diazepam rectal solution)
- Local effects are required, for example laxative preparations (e.g. bisacodyl or glycerol suppositories), or anti-inflammatory preparations (e.g. sulphasalazine or prednisolone suppositories).
- The oral dosage form is rejected because of palatability issues.

However, when administering rectal preparations to paediatric patients, there is a danger of the dosage forms being expelled prematurely. In addition, concordance and compliance may be lower than for oral dosage forms, as the rectal route of administration is poorly accepted by patients and caregivers in certain countries and cultures.

### 2.4.2 Dosage Forms and Formulation Considerations

Suppositories are the most common rectal paediatric dosage form. Other dosage forms include creams, ointments, gels, foams, gelatine capsules and small-volume (<20ml) or large volume (>67.5ml) solution or suspension enemas. Rectal dosage forms are currently often only available in doses suitable for adults and older paediatric patients.

Suppositories should be available in a variety of strengths for various age groups. The size of the suppository should be related to the patient's age. Typically, suppositories for infants weigh approximately 1 g, half the weight of the adult dosage form.

The volume of enemas should be related to their function (local or systemic effect) and to the age of the child. Volumes of enemas for systemic therapy in paediatric patients should be as small as possible to achieve accurate delivery, good absorption and absence of irritation. Volumes of 1-5 ml, depending on age and dose delivered, may be acceptable. The dose delivery device should allow simple delivery; the rectal tube should not cause injury and should be of a length appropriate for the age of the child. The use of scaled devices (pre-filled syringes with 'rectal tip') will facilitate individual dosing, in contrast to the 'all or none' devices, and may reduce the need for several strengths or dosages.

Excipients used in rectal dosage forms should not irritate the rectal mucosa of infants and children. For example, polyethylene glycol bases may lead to irritation of the rectal mucosa due to their hygroscopic nature, which may be reduced by moistening the suppository with water prior to insertion.

## 2.5 TOPICAL – TRANSDERMAL DELIVERY

### 2.5.1 Introduction

Rational dose delivery of topical dermatologicals and transdermal systems in order to achieve balance between efficacy, local and systemic safety is one of the major demands on formulations for the paediatric population. Clear differentiation between desired and adverse effects of topical and transdermal pharmaceutical forms is necessary.

- Penetration and permeation characteristics (topical *versus* systemic bioavailability) of active substances are strongly dependent on physiological factors such as skin site and skin condition as well as the characteristics of the vehicle (pharmaceutical availability).

- Important morphological and hence permeability differences exist between normal (mature) skin and that of a neonate (especially the pre-term infant).

    - At birth the dermis is normally only around 60 % of its adult thickness and maturation takes 3-5 months after birth.

- Once matured, infant skin presents less variability in comparison to adult skin. The thickness of the stratum corneum remains essentially the same but in neonates and infants the epidermis is perfused and hydrated to a greater degree than in adults.

- Permeation differences in relation to different application-sites of the body are similar to adult skin.

- Efficacy, local and systemic safety often correlate with the body surface area/weight ratio.
  - The surface area to body weight ratio in infants may be twice that of adults (see table 2.1).
  - Both physiological factors and surface area/weight ratio change greatly during the first years of childhood.

- Furthermore, infants have a reduced capacity for biotransformation and elimination of active substances including those absorbed by the cutaneous route.

In summary, better permeation of active drugs and other exogenous substances should be taken into account with topical formulations for neonates, infants and children and risk assessments should, therefore, be separate from those for adults.

**Table 2.1 Correlation between Surface area/body weight ratio *vs* Age**
(adapted from Werfel S, Boeck K, Abeck D, Ring J (1998) Besonderheiten der topischen Behandlung im Kindesalter, Hautarzt 49: 170-175)

| Age | Weight (kg) | Surface area ($cm^2$) | Ratio (surface/weight) ($cm^2$/kg) | Comparison (adult = 1) |
|---|---|---|---|---|
| newborn | 3.4 | 2,100 | 617.6 | 2.4 |
| 6 months | 7.5 | 3,500 | 466.7 | 1.8 |
| 1 year | 9.3 | 4,100 | 440.9 | 1.7 |
| 4 years | 15.5 | 6,500 | 419.4 | 1.6 |
| 10 years | 30.5 | 10,500 | 344.3 | 1.3 |
| Adult | 70 | 18,100 | 258.6 | 1 |

### 2.5.2 Consequences and considerations

*Topicals*

Topical bioavailability for dermatologicals is generally low so there is potential for large variations in bioavailability. Manufacturers should take into account skin changes during childhood and the increased surface area to weight ratio and develop appropriate age-related formulations and application doses.

- In paediatric patients below the age of 2 years (newborn, infants and toddlers) the application area of topical dosage forms should be restricted. For example, in the case of corticosteroids a 2-10 fold higher systemic exposure (even more in damaged skin) has been demonstrated.

- Water-impermeable materials (e.g. occlusive dressings, nappies, patches) as well as high lipophilic vehicles (e.g. paraffin-based formulations) that cover the application site may increase systemic exposure.

  - Occlusion may be useful when systemic availability of an active substance is wanted but should be avoided if systemic uptake results in an adverse reaction.
  - Thermoregulation and transepidermal water loss might be influenced drastically depending on the vehicle used, especially for neonates.
  - A careful risk/benefit evaluation is required.

- Fever and external heat (e.g. use of radiators, hot baths) may increase the rate of permeation.

Within a class of active substances, where systemic absorption should be avoided, the use of active substances with a high rate of metabolism inside the skin should be preferred.

*Transdermal patches*

Transdermal patches allow continuous, painless active drug permeation over hours or even days ("needle-free infusion") combined with high patient compliance. They have many of the features of a formulation of choice for the paediatric population. Systemic availability could be achieved for some active substances used in paediatric therapy by using transdermal patches yet this route of administration is rarely available. Typically, analgesics, sedatives, anti-emetics, cardiovascular and respiratory drugs need to be administered in a controlled manner. Reduction of skin barrier properties could be advantageous for the delivery of these active substances to the neonate. Few transdermal patches are currently authorised in the EU for use in paediatric patients and those available for adults are of inappropriate size and dosage delivery for paediatric patients.

- It is unlikely that a single transdermal formulation could cover the various skin properties during the evolving stages of skin maturation of neonates, infants and children such that individual case evaluation is necessary.

- Whilst most transdermal monolithic matrix type patches could be divided by the caregiver into smaller parts in order to adjust dosing of active substances to the specific requirements of the paediatric target group, preparations designed specifically for paediatric patients are preferred. As a minimum, cutting lines on the patch should be provided by the manufacturer to allow appropriate dosing.

- Transdermal membrane-type patches should never be cut into smaller parts. Destroying the membrane leads to uncontrolled delivery of the active substance and provokes 'dose dumping' with possible lethal consequences.

- Because of its standardized, reproducible delivery behaviour, a transdermal patch or system should always be favoured where systemic uptake of an active substance via skin is wanted.

  - Creams, ointments and gels for transdermal delivery should be considered only in cases where no adequate transdermal patch or system is available.
  - In most cases an additional occlusion of the formulation is needed, in order to influence the permeation characteristics or simply to protect the formulation from accidental removal, rubbing or touching.

Disadvantages of transdermal patches include deliberate removal by the child and suitable application sites, which cannot be easily reached by the child, should be investigated. The size of the patch should take account of the age of the child and adhesives should have low allergenic potential to avoid irritation and subsequent infection.

## 2.6 PARENTERAL ADMINISTRATION

This section focuses on substances delivered by intravenous injection and infusion, with brief notes on intramuscular, subcutaneous and intra-dermal injection together with trans-cutaneous administration with needle-free systems.

For seriously ill paediatric patients, and to reduce pain and fear of injections, the intravenous route is preferred and, if possible, injections are administered through an indwelling venous cannula. A variety of techniques can be used to limit the pain experienced when other routes of administration are used, particularly for immunisation (1-3).

### 2.6.1 Routes of intravenous administration

Venous access may be by small cannulae in peripheral veins; larger catheters with the tip located in central veins and semi-permanent central venous catheters with subcutaneous reservoirs will all be encountered.
Peripheral veins with comparatively slow blood flow will be irritated by a high osmotic load, extremes of pH and the chemical nature of some active substances and excipients. Phlebitis, thrombo-phlebitis or infiltration of the tissues may result with loss of the vein for therapy and possibly tissue damage (4).
When catheters are positioned in the central veins blood flow is fast and achieves rapid dilution of injected substances. Since there is such rapid dilution it may be unnecessary to dilute intravenous formulations given by the central route to the same extent as those given into peripheral veins.

- The ability to give more concentrated drugs may be very important when fluid intake is restricted.

  However, the rate of administration should take into account the potential for toxicity and adverse effects and rate of administration via central veins is unlikely to be different to the rate for administration via peripheral veins.

- Due consideration should be given to the potential route of intravenous administration (central versus peripheral) and instructions provided for additional dilution (if appropriate) relevant to the route of administration.

  The volume of additional diluent should be varied with the dose to be delivered so that the concentration of drug:diluent remains the same; an instruction ‘to dilute X times before administration’ should be given.

- Alternatively, instructions for injection of the undiluted product into a running infusion may be appropriate

  Compatible infusion fluids should be described and where appropriate should include glucose 5% and 10%, sodium chloride 0.45% and 0.9%, and combinations of glucose and saline.

- The preferred and maximum rates of administration should be stated in relation to the patient’s weight (e.g. X mg/kg/minute) if critical or the time period for administration should be stated (e.g. inject slowly over 5 minutes).

### 2.6.2 Formulation considerations for intravenous injections:

*Reconstitution and displacement volumes*

Many active substances for injection will be presented as lyophilised powders to be reconstituted before administration. Most doses for neonates, infants and children will require withdrawal of a dose volume, which is less than the total volume after reconstitution (5, 6).

- The recommended reconstitution volume should take displacement into account and should be an amount, which results in a drug concentration which simplifies calculation of proportions.

  Reconstitution instructions might state ‘add X ml Water for Injection to the Y gram vial to produce a solution containing A mg per ml’

In many health care systems, centralised preparation of injections for paediatric patients in syringes ready-to-use is encouraged to improve safety and reduce wastage (7).

- The chemical and physical stability of the reconstituted product should be stated when prepared in controlled (pharmacy aseptic suite) and uncontrolled (ward) conditions as defined in the Note for Guidance on the Maximum Shelf-Life for Sterile Products for Human Use (CPMP/QWP/159/96).

  The stability of any further dilution required to render the product suitable for administration should also be stated (Note for Guidance on In-Use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99)).

*Osmolality and pH*

Excipients may contribute to the body's osmotic load and cause serious systemic adverse effects in sick neonates, infants and children. Hyper-osmolar injections and extremes of pH may irritate small peripheral veins and produce thrombophlebitis and extravasation. Hypo-osmolar injections may induce haemolysis.

- Careful consideration must be given to the concentration and nature of excipients.

- An iso-osmotic concentration is preferred and should be achieved by adding suitable tonicity adjusting agents such as sodium chloride or glucose to the formulation or by recommending appropriate dilution prior to administration.

- Hyperosmolar injections may be appropriate for central venous administration without further dilution. The rate of administration must be stated.

- Instructions for dilution (if necessary) of injections for peripheral vein administration must take into account potential for effects on the child's fluid and sodium balance.

- Preparations presented as infusions should be of neutral pH and iso-osmotic unless intended to be co-infused with other solutions. Clear warnings must be given about the need for dilution or co-infusion.

*Presentation*

If paediatric injections are produced in a variety of sizes and concentrations (in relation to the age and weight of patients to be treated), doses can be measured accurately, wastage can be minimised and the good practice of discarding the remainder of solution in vials prepared in uncontrolled conditions is more likely.

If very small volumes must be measured to achieve the dose, due regard must be given to the way in which the volume can be measured.

- It can be helpful to specify the size of syringe that permits accurate administration.

- Serial dilutions to achieve measurable volumes are particularly prone to error and should be avoided by providing appropriate vial sizes and concentrations.

### 2.6.3 Fluid requirements

The daily allowance of fluid for paediatric patients receiving intravenous therapy is related to age and weight. For example, a 1 kg neonate may only receive 150 ml per day to include all nutritional requirements as well as therapy. The volume and electrolyte content of intravenous infusions and injections may contribute critically to the daily intake.

- Approximate daily fluid and sodium requirements for paediatric patients of various ages can be calculated from table 2.2.

- If several intravenous drugs are required and they require dilution and flushing into the circulation, the child's fluid and sodium requirements may easily be exceeded or be so high that nutrition is compromised.

- When making recommendations for dilution and flushing of intravenous drugs, manufacturers should take into consideration that several intravenous drugs may be required when paediatric patients are seriously ill. The smallest practical volumes should be quoted. Residual volumes in giving sets and intravenous lines may be significant for neonates, and special low volumes medical devices for this purpose should be considered.

- Careful consideration must be given to the volume of injections in relation to age and weight. The need for dilution and flushing must also be carefully assessed in relation to osmolality, pH, and chemical irritancy of the active substance and excipients.

2.6.4 Subcutaneous/intradermal/intramuscular administration

Some injections can be delivered by subcutaneous or intramuscular injection whilst others will be for use only by one route or the other..
Needle length in relation to age and weight are important in ensuring the correct site of injection (9, 10).

*Subcutaneous injection*

Automatic subcutaneous needle insertion may be less painful than manual insertion and can improve compliance with long-term therapy (11).
The site of injection and injection volume are important. The injection size should be kept small and should not exceed 1 ml for older children (12).
Consideration should be given to the formulation in relation to pain on injection (13, 14).

- Using a physiological pH is preferred if the active substance is stable.

- When non-physiological pH must be used the lowest possible buffer strength is associated with least discomfort.

- Buffers containing citrates are associated with local pain.

*Intradermal injection*

The intradermal route may be required for diagnostic agents such as Tuberculin PPD, for vaccines such as BCG and occasionally for corticosteroid depot preparations.
The technique for accurate intradermal injection is difficult especially for neonates, infants and toddlers.

*Intramuscular injection*

Intramuscular injections are generally painful for children so the intravenous route may be preferred if several regular injections are required. Muscle mass in children is variable and the depth of muscle and fat layers will vary. Absorption may be poor and complications such as muscle contractures and nerve injury may follow if the appropriate site of needle insertion, needle size and angle of injection are not effectively selected for the age and size of the child and the nature of the preparation (15-17).

- The potential for a preparation to irritate or damage muscle should be assessed. In vitro models have been described (18-22).

    - Liposomal encapsulation can reduce myotoxicity.
    - Cosolvents such as propylene glycol and ethanol have additive myotoxic effects whilst polyethylene glycol 400 may have protective effects.

- The nature of buffers and pH are important determinants of myotoxicity.

- Injection volumes should be small and should not exceed 1 ml at a single site (23).

- Addition of local anaesthetic such as lidocaine may reduce incidence and duration of pain from intramuscular injection. Consideration should be given to recommending the use of local anaesthetic solution as the diluent (24).

2.6.5 Transcutaneous delivery

Some paediatric patients receiving regular injections, for example, of growth hormone, express a preference for needle-less systems using compressed air to fire a fine jet of solution, which penetrates the skin with minimum discomfort (25-6).

- Transcutaneous administration should be considered when therapy requires frequent administration, provided acceptable bioavailability can be demonstrated.

2.6.6 Other routes of administration

Paediatric patients, like adult patients, may benefit from other parenteral routes of administration but they may not be as well tolerated. Thus, intrathecal injections must usually be administered under general anaesthesia.

- In palliative care, subcutaneous infusion may be valuable.

- Patient-controlled analgesia or nurse-controlled analgesia for young children and epidural pain relief are each gaining in popularity.

- Intra-osseous administration is used in emergency situations when venous access cannot be established easily.

  - When active substances are likely to be used in emergency situations such as resuscitation and intensive care, suitability for intra-osseous administration should be established.

- Because of the issues around pain and co-operation, routes of administration that do not involve injection should be explored as alternatives.

  - Rate and extent of absorption should be similar to injection although the time required establishing venous access should be taken into account.
  - Buccal or intranasal administration may be suitable alternatives.
  - Transdermal administration should be considered as an alternative to intravenous infusion.

**Table 2.2 Approximate normal daily fluid and sodium requirements for paediatric patients of different ages (8)**

| **Body weight** | **Volume per 24 hours** |
|---|---|
| Less than 3 kg | 150 ml/kg<br>(but starting at 40-60 ml/kg for newborn) |
| 3-10 kg | 100 ml/kg |
| 11-20 kg | 1000 ml plus 50 ml/kg for each kg from 11-20 kg.<br>e.g. 15 kg = 1000 + (5x50) = 1250 ml |
| Greater than 20 kg | 1500 ml plus 20 ml/kg for each kg above 20 kg<br>e.g. 30 kg = 1500 + (10x20) = 1700 ml |
| Adult female | 2000 ml |
| Adult male | 2500 ml |

| | |
|---|---|
| **Sodium requirement** | Approximately 3 mmol/kg/day |

## 2.7 PULMONARY ADMINISTRATION

### 2.7.1 Introduction

Inhalation is a suitable way to administer active substances to the lung. It is the preferred route of administration for patients with asthma. Other diseases such as pulmonary infection in cystic fibrosis can also be treated locally by inhalation. In the future inhalation might become more important for the application of active substances for systemic treatment. The following statements are mainly concerned with the local therapy of asthma.

Recommendations and comments for the selection of appropriate delivery devices in relation to age are available (1-9). The use of dosage forms for asthma in children should be in line with the recommendations in the guidelines (10). However, in young (0-5 years) children, little or no evidence is available on which to base recommendations (3).

### 2.7.2 Advantages and disadvantages

Advantages of the inhalation route over the oral route of administration include the avoidance of the hepatic first-pass metabolism. Inhalation might be an alternative route to parenteral application for systemic treatment, e.g. with peptides and proteins. Compared to the parenteral route, pain during application can be avoided (see section 2.1).

The fraction delivered to the lung depends on several factors. One important factor is the ability of the patient to use the device correctly. Dependent on their age children will have more or less difficulties with some of the devices (see 2.7.3). Problems with the coordination of the inhalation for pressurised metered dose inhalers and the ability to inhale strong enough for dry powder inhaler devices determine the effectiveness of getting the drug into the lung.

### 2.7.3 Dosage Forms and Formulation Considerations

- Pressurized Metered Dose Inhalers (pMDI)
  pMDIs are efficient but require considerable coordination of the actuation of the device and the inhalation action (i.e. press and breath), which precludes their use in young children. Many children can be trained to use a breath-activated pMDI, which is triggered automatically to release the metered dose at the onset of inhalation (1).
  - Spacers and Holding Chambers

  The use of spacers and holding chambers with a pMDI avoids issues of patient co-ordination and means that less medication impacts on the oropharynx. Using a face mask attached to a holding chamber facilitates the use of pMDI with very young infants, although they may sometimes reduce the dose reaching the airways (1). Wherever possible, children should inhale through the mouth rather than the nose. The suitability of a selected spacer/holding chamber with a specific pMDI should be checked in each case (i.e. information provided in the patient information leaflet).

- Dry Powder Inhaler (DPI)
  DPIs can be efficient delivery systems for children old enough to achieve the necessary inspiratory flow. The inspiratory flow required to allow the powder to be inhaled varies from device to device.
  New DPIs appearing on the market may provide dispersive energy and will assist de-aggregating the powder. Subject to suitable evidence, these devices might be appropriate for younger children.

- Nebuliser

Traditional air compressor nebulisers are bulky and inefficient aerosol delivery systems. Newer nebulisers of both air compressor and other designs are more compact. They may offer more efficient delivery of medication to the lung because of novel features including computer control.

New devices for nebulised medicinal products are available, which are as convenient as pMDIs concerning the size and the duration of inhalation. The whole dose is nebulised instantly and can be inhaled at once. This type could also be classified as metered dose liquid inhalers.

## 3. AGE, DEVELOPMENT AND DOSAGE FORMS OF CHOICE

One of the most important issues in the development of medicinal products for paediatric patients is the most appropriate dosage form in relation to age. Few studies have been performed to survey the use of different formulations in paediatric patients. In particular, there are concerns about the age at which young children can safely swallow conventional tablets and capsules. Whilst this has not often been examined directly in the literature, there is indirect evidence from an examination of prescriptions for different dosage forms in relation to age (1, 2) and anecdotal reports of very young children being trained to manage oral solid dosage forms for chronic illness such as leukaemia and HIV (3). Suppositories may be prescribed more commonly for paediatric patients < 5 years whilst the prescription of dosage forms such as inhalers and topical treatments remains relatively constant in relation to age through childhood (1).

A matrix combining different age groups, routes of administration and dosage forms has been developed to assist in answering this question. The age classification is according to the guideline on the clinical investigation of medicinal products in the paediatric population (CHMP/ICH/2711/99) (4) with the exception that 'children' have been further divided into pre-school children (2y-5y) and school children (6y-12y) because of the significant changes in ability to handle some dosage forms between 2-12 years of age.
The matrix is not an in depth, evidence-based piece of work, but was constructed based on a questionnaire shown to about 40 persons from several European countries, namely hospital paediatricians, pharmaceutical scientists and parents. In some cases there was wide variation in the answers. The original questionnaire was simplified and summarised in order to present the matrix. The table is not intended as a recommendation for the development of a specific dosage form for an age group, but reflects some general aspects of acceptability of the various dosage forms. Clearly, further research in this area is required.

The classification of the dosage forms is given separately for the important routes of administration. The various routes of administration and the respective dosage forms are discussed in other sections of the document. The matrix mainly contains conventional dosage forms. Other dosage forms, which might be of special value for paediatric patients are mentioned in the other sections.

The code used in the matrix can be interpreted in the following way:

- For the early ages the code indicates mainly the applicability of the route and the dosage form:

  1 not applicable,
  2 applicable with problems
  3 probably applicable, but not preferred
  4 good applicability
  5 best and preferred applicability,

- For the higher ages more or less all dosage forms might be principally applicable, but with increasing age the preference of the children becomes more important:

  1 not accepted
  2 accepted under reserve
  3 acceptable

4 preferred acceptability
5 dosage form of choice

From the left to the right columns in the table, the focus shifts from the applicability to the preference.

The matrix can only be a rough guide. Naturally, paediatric patients (also of the same age) behave and feel differently and they have different ability to handle dosage forms. The acceptance of certain dosage forms depends very much on the child's mood, illness, influence of their caregivers, cultural and/or regional habits. Within the same type of dosage form huge differences in acceptance according to the properties of the drug(s) and the formulation might be seen. For example, if a suspension contains a bitter tasting substance, the acceptability highly depends on the concept and performance of the taste masking strategy. Thus, a generalised judgement of applicability and acceptability of a dosage form might not be applicable to all paediatric patients in the respective age group and all individual formulations of a certain type of dosage form. Nevertheless, the matrix can generally indicate preferred routes and formulations as a function of the child's age.

**Table 3.1 Matrix: Route of administration/dosage form vs. Age**

| **Route** Dosage Form | ***Preterm newborn infants*** | ***Term newborn infants (0d-28d)*** | ***Infants and Toddlers (1m-2y)*** | ***Children (pre school) (2-5y)*** | ***Children (school) (6-11y)*** | ***Adolescents (12-16/18y)*** |
|---|---|---|---|---|---|---|
| **Peroral** | | | | | | |
| Solution/ Drops | 2 | 4 | 5 | 5 | 4 | 4 |
| Emulsion/ Suspension | 2 | 3 | 4 | 5 | 4 | 4 |
| Effervescent DF* | 2 | 4 | 5 | 5 | 4 | 4 |
| Powders/ Multiparticulates | 1 | 2 | 2 | 4 | 4 | 5 |
| Tablets | 1 | 1 | 1 | 3 | 4 | 5 |
| Capsules | 1 | 1 | 1 | 2 | 4 | 5 |
| Orodispersable DF | 1 | 2 | 3 | 4 | 5 | 5 |
| Chewable tablets | 1 | 1 | 1 | 3 | 5 | 5 |
| **Nasal** | | | | | | |
| Solution | 3 | 4 | 4 | 4 | 4 | 4 |
| Semisolid DF | 2 | 3 | 3 | 4 | 4 | 4 |
| **Rectal** | | | | | | |
| Suppositories | 4 | 5 | 5 | 4 | 3 | 2 |
| Rectal Enema | 5 | 4 | 4 | 3 | 3 | 2 |
| Rectal capsules | 2 | 3 | 4 | 4 | 4 | 3 |
| **Topical/ transdermal** | | | | | | |
| Ointment, Cream, Gel | 4 | 4 | 4 | 5 | 5 | 5 |
| Liquid DF | 4 | 4 | 4 | 5 | 4 | 4 |
| Transdermal Patch | 1 | 2 | 2 | 4 | 4 | 5 |
| **Parenteral** | | | | | | |
| i.v. Solution | 5 | 4 | 4 | 4 | 4 | 3 |
| i.m. | 3 | 3 | 3 | 4 | 4 | 3 |
| s.c. | 4 | 4 | 4 | 4 | 4 | 3 |
| Pump system | 5 | 4 | 4 | 4 | 4 | 3 |
| **Pulmonary** | | | | | | |
| Nebuliser | 2 | 3 | 4 | 5 | 4 | 3 |
| MDI / Spacer | 1 | 3 | 4 | 5 | 4 | 4 |
| DPI | 1 | 1 | 3 | 4 | 5 | 5 |
| **Ocular** | | | | | | |
| Eye drops | 3 | 4 | 4 | 4 | 5 | 5 |
| Semisolid DF | 2 | 3 | 4 | 4 | 4 | 4 |

*DF: Dosage Forms

## 4. EXCIPIENTS

Although excipients should be pharmacologically inactive, they may indeed cause adverse effects. Particularly when used in paediatric formulations, it has to be kept in mind that the physiology of neonates and infants differs considerably from that of adults. They may not be able to metabolise or eliminate an ingredient in a pharmaceutical product in the same manner as an adult (1).

Several EU guidelines related to the use and declaration of excipients have been published and should be consulted. Additional information may be found in documents published by the European Commission (15, 16) and the US Food and Drug Administration (FDA).

The following groups of excipients and the substances listed are not exhaustive, but aim to reflect the issues most likely to be relevant specifically to paediatric patients. These issues should also be taken into account when designing dosage forms for adults that may have application in paediatric practice.

### 4.1 Preservatives

Benzyl Alcohol / Benzoic Acid / Benzoates

Benzyl alcohol is often used as a preservative in injectable medicinal products. It must not be given to neonates due to their immature metabolism. In developing pharmaceutical preparations for use in young paediatric patients up to three years old, benzyl alcohol should be carefully evaluated and may best be avoided (2-4). It may cause pain on injection. Benzoic acid, sodium benzoate and potassium benzoate when used in parenteral dosage forms may increase the risk of jaundice in neonates.

### 4.2 Sweeteners

Sucrose

Sucrose is the most commonly used sweetening agent. It is a disaccharide that is readily hydrolysed in the intestine to the absorbable mono-saccharides fructose and glucose. It should be avoided for paediatric patients suffering from hereditary fructose intolerance. Formulations with high amounts of sugar should be avoided in therapy of paediatric patients, suffering from diabetes (5). For preparations intended for long-term therapy large amounts of sucrose should be replaced by sugar-free formulations, since sucrose causes a decrease in dental plaque pH, dissolving tooth enamel and promoting dental caries.

Fructose

Fructose causes an elevation in blood glucose concentration and should therefore be avoided in patients suffering from diabetes. It is also contraindicated in patients with hypoglycaemia or hereditary fructose intolerance (3). It may cause laxative effects when administered orally at high doses.

Sorbitol, Xylitol

Sorbitol, and xylitol are mono-saccharides and are not readily absorbed from the gut and therefore are considered safe for diabetes patients. Sorbitol and xylitol may cause osmotic diarrhea (6). Since sorbitol is metabolised to fructose, it is contraindicated in paediatric patients with hereditary fructose intolerance and hypoglycaemia – in severe cases it may cause damage of the liver accompanied with coma resulting in death in those patients. Especially intravenous administration of sorbitol should be avoided (7).

Aspartame

Aspartame, a dipeptide of aspartic acid and a methyl ester of phenylalanine, is 150-200 times as sweet as sucrose. The phenylalanine component may be harmful in patients with phenylketonuria and contra-indicated in homozygous autosomal recessive patients (6). Rare hypersensitivity reactions have been reported. Cross-reactivity with sulfonamides can occur.

### 4.3 Fillers and solvents

Lactose
Lactose is a disaccharide of glucose and galactose, and is absorbed after hydrolysis by intestinal lactase (6). In infants and young children lactose intolerance may be associated with severe prolonged diarrhoea, dehydration, and metabolic acidosis (8). Although it is difficult to attribute these symptoms to the intake of such small lactose amounts used in formulations, sensitivity to lactose varies widely in severity and the intake of considerably less than 3 g may provoke the described symptoms (8).

Ethanol
Ethanol is a common solvent in oral liquid preparations. There are severe acute and chronic concerns in the use of ethanol containing medicinal products in the paediatric population, like acute intoxication with accidental overdose and chronic toxicity associated with routine use for chronic medical conditions (8). Acutely, the co-administration of ethanol may alter drug adsorption or metabolism and may result in drug interaction. Adverse effects to the Central Nervous System are commonly reported, arising with blood ethanol concentrations in the range of 1 – 100 mg/100 ml. The effect on the hepato-renal function of elevated ethanol concentration in long-term treatment has never been studied in the paediatric population. Research-based clinical parameters to establish "safe" or acceptable intake thresholds are conspicuously wanting (9).

Propylene Glycol (2, 8)
Propylene glycol is used as a solvent in oral, topical and injectable medications, often for substances, which are not highly soluble in water, e.g. phenobarbital, phenytoin and diazepam. It is also commonly used in injectable multivitamin concentrates. Paediatric patients below 4 years have a limited metabolic pathway (alcohol dehydrogenase), therefore accumulation of propylene glycol can occur in the body. For example, it has been shown that neonates have a longer propylene glycol half-life (16.9 hours) compared to adults (5 hours). Products containing high levels of propylene glycol should not be administered to paediatric patients below the age of 4 years. Main toxic action is depression of the central nervous system. High osmotic pressure may cause laxative effects. Topical administration has been reported to cause contact dermatitis (10).

### 4.4 Colouring Agents

The numbers of colouring agents that are globally acceptable from a regulatory perspective are limited. Generally, paediatric patients prefer brightly coloured preparations. However, colouring agents should be avoided in paediatric formulations unless necessary (e.g. to cover drug-related unpleasant colour of a liquid product), as many colouring agents have been associated with hypersensitivity and other adverse reactions. Most colouring agents used in pharmaceutical oral formulations belong to one of the following groups: azo dyes (e.g. tartrazine, sunset yellow and new coccine)), quinoline dyes (e.g. quinoline yellow), triphenylmethane dyes (e.g. FD&C blue) and xanthene dyes (e.g. erytrhosine) (6). Many side effects of colouring agents in the paediatric population have been reported in the literature (6,8,11,12). Acceptable daily values for young children (less than three years old) are presented in a European Commission report (16) .

### 4.5 Coating Materials

Cases of fibrosing colonopathy in children have been reported for high-strength pancreatic enzyme formulations coated with a methacrylic acid and ethylacrylate copolymer (13-14).

## 5. TASTE, SMELL AND TEXTURE

Apart from the taste and smell of the preparation there are many other potentially important parameters which determine whether a preparation will be accepted by the child. Texture of the

formulation in the oral cavity plays an important role, although the effects of texture have received little attention in pharmaceutical development since preventive measures are limited. Appearance also contributes to the overall acceptability and may even influences basic perception of the flavour.
General information on the physiology and perception of taste, smell and flavour and on taste-masking can be found in the bibliography.

## 5.1 The physiology of taste and olfaction in children

Taste sensations arise from stimulation of specialized cells grouped in small clusters called taste buds which exist in small bumps on the front of the tongue, in folds on the side of the tongue, and in circular grooves on the back of the tongue surface.
The human foetus appears to have specialized taste cells at about the $7^{th}$ or $8^{th}$ week of gestation, with structurally mature taste buds visible at 13 to 15 weeks. In contrast, olfaction develops postnatally. Odours are detected within hours of birth. Changes in respiration and salivation can be observed, and responses become more robust during the first few days after birth. Infants also show sensory functions characteristic of mature olfaction, such as decrements in response during repeated presentation of an odour and enhanced responding due to a previous presentation of a contrasting odour. However, although the infant appears equipped to smell things, the affective responses to pleasant/unpleasant odours do not appear in children until the age of about 5; after age of 6 the adult pattern may be observed (1-3).

## 5.2 Recommendations for selection and use of flavours in paediatric formulations

### 5.2.1 Recognition of the flavour by the target population

It has been reported that children have greater difficulties to recognize tastes in mixtures than adults due to their limited analytical skills in perceptual tasks. Their analytical ability evolves in pre-school years and increases until adolescence. However, their ability to recognize a flavour may also be affected by the concentration of the flavour in the formulation and the appearance of the medication itself. For example, a strawberry flavour-containing formulation was identified as chocolate because of its brown colour, indicating a strong association between colour and flavour.
Whether children can analyse and recognize more than one flavour component in a taste mixture is unknown and the concentration of each of the flavours may affect a child's assessment.

Enhancing the degree of recognition by avoiding unusual flavours and complex taste mixtures increases the probability that a formulation will be accepted by children.

### 5.2.2 Acceptance of the flavour by the target population

Social factors, such as food selection of adults and peers can have strong effects on children's flavour preferences. Cultural influences can also have strong effects on children's attitudes and preferences toward even the basic tastes and flavours. Market research has revealed standard combinations of specific sweeteners with relevant flavours, which may vary by country and target market. National favourites include "bubble-gum" and "grape" in the United States, "citrus" and "red berries" in Europe and "liquorice" in Scandinavia. A bubble-gum or cherry flavour in combination with a high intensity sweetener may suit the US paediatric market, while a less intense sweetness may be more appropriate for Japan.
Children may find unpleasant and reject irritating sensations in the mouth such as effervescence or peppermint. Peppermint may be described as "spicy" or "hot" and rejected in the same way as bitter tastes.

For selection of the most suitable flavour for a paediatric medication, the type of flavour (acid, alkaline, bitter, salty or sweet; see Table 5.1) as well the health condition of the target population have to be considered (Table 5.2).

**Table 5.1: Flavour type**

| Basic sensation | Flavour to cover this taste |
|---|---|
| Acid | cherry, lemon, lime, mandarin, orange, strawberry |
| Alkaline | banana, caramel, cherry, liquorice, passion-fruit, peach |
| Bitter | cherry, chocolate, grapefruit, liquorice, strawberry, peach, raspberry, tutti-frutti |
| Salty | caramel, grapefruit, lemon, orange, vanilla |
| Sweet | banana, caramel, cream, chocolate, grape, vanilla |

**Table 5.2 Flavour preferences in Europe as a function of the disease of the target population**

| Condition | Associated flavour |
|---|---|
| Pain, fever, allergy, infections | cherry, strawberry, banana, caramel |
| Vitamin deficiency (Multivitamins) | blackcurrant, lemon, lime, mandarin, orange |
| Indigestion (Antacids) | lemon, lime, orange, peppermint |

5.2.3 Sweetness of paediatric formulations

Paediatric patients are able to recognize sweetness from an early stage of life and are also able to recognize sweet taste in mixtures and estimate the strength or degree of sweetness. The same is true for saltiness. However, their ability to distinguish and recognize both tastes in a mixture depends on the age of the child but is limited compared to adults either due to immature analytical abilities or because the gustatory system processes mixtures differently to that of the adults (4).
Children seem to prefer higher levels of sweetness than adults and there appear to be transient gender differences only in children with 4-12 year-old girls more sensitive to sweetness and saltiness than boys.

5.2.4 Effectiveness of sweeteners to mask the bad taste

High concentrations of intense sweeteners such as sodium saccharine or aspartame are sometimes used but may be unsuccessful in masking bitter taste in paediatric formulations. These sweetening agents appear to develop a bitter aftertaste at high concentrations. The intensity of sweetness and bitter taste masking capacity at relative low concentration levels may be enhanced by the addition of a sodium salt to the mixture, presumably by blocking bitterness and thereby releasing sweetness.

## 5.3 Methods to assess the acceptability of a medication

Taste and smell can be quantitatively evaluated using indirect analytical methods and by taste/smell sensors or qualitatively by taste panels. More detailed information is available in Annex 2 and the bibliography.

5.3.1 Qualitative evaluation of the acceptability by a taste panel

Consumer testing by pre-screened users with an interest in the product quality is acknowledged as the best population to assess a product. Children are consumers of medicinal products with sensory differences to adults. Children are, therefore, a population regarded as the most suitable panel for taste assessment of paediatric formulations. It may be considered ethical to test some products with volunteer children but others should only be tested in children with the disease to be treated by the active drug. More detailed information is available in Annex 2 and the bibliography.

## 6. MODIFIED RELEASE PREPARATIONS

MR preparations can be useful for children who would otherwise need to take medication whilst at school or during the night. Transdermal preparations can provide a useful, prolonged effect but the different levels of skin permeability with age should be taken into consideration. MR injections can reduce the dosing frequency significantly, which is important for avoiding pain (see section 2.5). In oral preparations once daily formulations can be beneficial for compliance. However, the different transit times in paediatric patients and the different physiological conditions, e.g. the pH in the stomach, should be taken into consideration when designing a MR formulation.

MR preparations should be capable of meeting the dosage requirement of a wide range of ages. For solid dosage forms this can be achieved by the use of multiparticulate formulations, e.g. prolonged release granules with a specified dose per granule. The small particles can also be swallowed easier than monolithic dosage forms, and allow adjustment of the dose and thus the use of a product applicable to adults in the paediatric population. In liquid MR formulations the active substance is usually incorporated in or bound to small particles, e.g. pellets or resin particles. Oral suspensions can contain particles or pellets with modified release. The size of the pellets should be limited, and patients must not chew these pellets. Knowledge about suitable particle size related to age is lacking. Depending on the size, multiparticulate MR dosage forms might also be deliverable through tubes.

The specific surface area of multiparticulates is higher compared to monolithic dosage forms. If the multiparticulate formulation has to be coated, the amount of coating polymer and other related excipients exceeds the amount required for a monolithic dosage form. This has to be considered in the choice of suitable excipients. A risk assessment of polymers and other excipients, e.g. plasticizers is important with respect to the administered dose and the weight of the child.

Due to the different principles and excipients used for achieving MR it should be stated whether the MR dosage form can be dispersed in a liquid or even crushed prior to use. It should also be noted, whether the MR dosage form can be given together with liquid or soft food. Suitable types of common liquids and foods should be specified.

## 7. DOSE DELIVERY DEVICES

### 7.1 Introduction

Devices for the delivery of paediatric medicinal products should allow accurate dose measurement and simple, controlled administration.

### 7.2 Design of the device

#### 7.2.1 Household spoons

Household spoons should not be recommended as dose delivery devices for children’s medicinal products.
If a spoon is considered to be appropriate for dose delivery a 5 ml spoon designed and manufactured to an appropriate international, EU or national standard should be provided by the manufacturer.

#### 7.2.2 Droppers

Delivery of liquid medicinal products as a small volume measured as drops may be convenient, particularly for infants and young children. However, the accuracy of dosing depends on several factors, especially the angle at which the dropper bottle is held and the viscosity and density of the preparation.

Accuracy of drop delivery should be confirmed by standardised laboratory tests and in-use testing. Information, preferably pictorial, about the method of use must be provided in a patient information leaflet. Devices which provide greater guarantees of accurate dose delivery should be considered.

#### 7.2.3 Measuring spoons and cups

Validated measuring spoons and cups are convenient for toddlers and children who can use them without spilling but it is difficult to control administration if the child is uncooperative.
They are commonly available in a total volume of 10 ml, with and without calibration lines for lower volume, i.e. 5 and 2.5 ml. Measuring spoons and cups can be used for all liquid preparations such as suspensions and solutions. Accuracy of measurement will depend on physical properties of the liquid such as viscosity and surface tension and interpretation of graduations and meniscus by the user. Measuring spoons and cups are generally not recommended for the administration of drugs with a narrow therapeutic index.

#### 7.2.4 Cylindrical measuring spoons

Spoons which are attached to a small measuring cylinder may be easier to use without spillage than traditional medicine spoons or cups.

#### 7.2.5 Graduated Pipettes and Oral Dosing Syringes

Graduated pipettes and oral syringes are particularly convenient for infants and young children who are not able to use either spoons or cups and allow accurate dose measurement and controlled administration to the buccal cavity for all ages. These dosing devices are recommended for medication with a narrow therapeutic window where accurate dosing is mandatory. Oral syringes must not be capable of accepting a needle or connecting to intravenous devices; thus preventing accidental parenteral injection of the liquid. Syringe caps are particularly dangerous for young children; suitable warnings must be given in product information.
Graduated pipettes intended for administration directly into the mouth must not be made of material that could break or cause damage.

### 7.3 Dosing accuracy

The device selected should be appropriate to the volumes to be measured, therapeutic index of the active substance, type and taste of formulation and ease of administration in practice. Foaming after reconstitution or in use may affect accuracy of measurement and appropriate information and warnings should be given.

The facility to accurately measure small volumes of injections intended for newborns and young children is of particular importance. Concentrations of active substances should be such that the dosage volumes required can be measured with standard syringes and without further dilution. If dilution is required after measurement and prior to administration it must be remembered that a significant extra quantity of active drug may be contained in the hub of the syringe so appropriate instructions must be given. Failure to dilute very small volumes prior to intravenous administration or to flush them into the system may result in delays in delivering the drug or failure to deliver the whole quantity because of loss within administration apparatus.

### 7.4 Additional Aspects

To avoid potential for error, graduations on dosing devices should only be stated in ml or fractions of a ml. If markings in other units can be justified (e.g. mg) the device must be labelled for use with that product only.

Design and labelling of the device should enhance use and should be evaluated by testing. Compatibility of all components of the device and labelling should be established, as should resistance to common washing procedures. Information should be provided to the user.

## 8. ADDITIONAL ISSUES TO BE CONSIDERED

This section should be read in conjunction with Annex 1 concerning the risks associated with the manipulation of adult medicinal products. The manipulation of adult medicinal products for paediatric use should be the last resort, but at the same time it is recognised as an unavoidable and necessary operation in many cases. Healthcare professionals who are performing these operations often do so with a minimum of information, and are often forced to rely on their professional art and general knowledge of pharmaceutical compounding science. Specific technical information relating to particular new proprietary products or substances rests, for the most part, in the hands of the pharmaceutical company which has developed the adult medicine. Such information would obviously be of value to healthcare professionals preparing paediatric dosages.

Companies are encouraged to make available as much relevant information as possible, for example

- Primary physicochemical data on the active substance: solubility and stability in common solvents, pH-solubility and stability profile, microbiological aspects, potential for solid-state transitions in suspension.
- Specific Paediatric Formulations: those which have been studied and validated together with their shelf life, storage conditions, compatible preservative systems etc.
- Common foods and drinks which are compatible with the powdered tablets or capsule contents from the point of view of stability and taste.
- Aspects of the adult medicine which may be a problem in the paediatric population, e.g. excipients, pH, osmolality.
- Critical functional components of dosage form (e.g. enteric coat / or modified release system) and whether they can safely be manipulated, or the dangers this would involve (see Annex 1.2).

In essence, the pharmaceutical industry should be aware that an ‘adult’ formulation may be manipulated for paediatric use and provide any such information about the product that would allow the pharmacist to design a satisfactory formulation. Depending on the evaluation of such data by the competent authorities, validated formulations for extemporaneous dispensing may be considered acceptable for inclusion in the SPC and package leaflet.
As a useful addition to these measures, the industry should also consider making available their pure ‘qualified’ active substances, in order to improve the quality of extemporaneous preparations and reduce the need for high-risk manipulations of finished adult products (See Annex 1, 1, iii)
Furthermore, pharmacists may wish to test these non-standard formulations. It would be helpful if relevant testing information (e.g. a stability-indicating assay method) was made available on request by a pharmacist.

## ANNEX 1

### Risks associated with manipulation of 'adult' dosage forms for administration to paediatric patients

The purpose of this Annex is to indicate to the pharmaceutical industry the way in which authorised dosage forms are manipulated to facilitate administration to paediatric patients or to extemporaneously prepare suitable paediatric dosage forms from adult presentations. Given this information the industry can have a better understanding of the information that could be provided to improve the quality, safety and efficacy of such manipulations during the time that they are necessary and unavoidable.

### 1 Background

Many medicinal products are authorised only for adult use and contain no validated provisions in the SPC for paediatric use. In these cases where the adult-only product may also be of benefit in the paediatric population, a number of practices have evolved to manipulate these adult medicinal products in order to render them suitable for dosing to paediatric patients. e.g. halving or quartering tablets, crushing tablets into powders etc.
In the practical world of paediatric pharmacy such practices have become established and indeed necessary. Usually there is little information on the bioavailability of the manipulated dosage form. Whilst the objective of this document is to encourage the pharmaceutical industry to develop authorised ready-made paediatric dosage forms which do not need such manipulations, the CHMP recognises that until such time as medicinal products which are clearly useful in paediatric patients are legitimately authorised and presented in a suitable form for this population, there will remain a gap where pharmacists and caregivers may need to manipulate adult medicinal products for the benefit of paediatric patients. Some general points may be noted:

i. Only the simplest manipulations (e.g. breaking scored or cutting un-scored tablets, crushing tablets or opening capsules) lend themselves to domiciliary use on an individual dosage basis. Health and safety of the carer must be considered.
ii. A common situation is likely to be the preparation of a program of doses by healthcare professionals in a hospital or community pharmacy setting, and most of what follows relates to this context (the sophisticated manipulation of adult medicinal products involving a change of pharmaceutical form and dosage should only be performed by healthcare professionals in a pharmacy).
iii. Manipulation of adult medicinal products into paediatric forms should preferably be regarded as a secondary option, to be performed when the necessary qualified raw materials, e.g. pure active substance, are unavailable. Qualified in this context means from a source that is used in a relevant EU-marketed medicinal product where the quality aspects have been evaluated and independently validated.
iv. In general, the SPC for the product in question should always be checked by the health care professional for the presence of excipients likely to be a problem in paediatric patients, particularly neonates.
v. Since the adult medicine will probably already contain excipients, reformulation for paediatric use should not add unnecessarily to this burden, i.e. it should be kept as simple as possible by avoiding additional excipients, e.g. extraneous colouring matter, etc. Due consideration should be given to active substance/excipient compatibility.
vi. It would be useful to pharmacists if the pharmaceutical industry could provide relevant physical/chemical/microbiological information to provide greater confidence in the quality of the manipulated formulations and to reduce the risks involved (see Chapter 8 for further details).

These manipulations come under the heading of magistral (extemporaneous) preparations. Such magistral products are indeed within the law, as foreseen in the EU legislation relating to medicinal

products, but are exempt from the normal data requirements necessary to support an application for a marketing authorisation. Liability for the magistral preparation seems to be different in the Member States, but as might be expected, responsibility rests mainly on the 'manipulators' themselves. It is acknowledged that in a hospital context, or in the hands of professionals such as pharmacists, the risks will be reduced as much as possible and weighed against the benefits of treatment (and the dangers of withholding treatment) to enable a responsible decision to be taken.
The following list of manipulations is not exhaustive, it serves chiefly to highlight the potential risks involved with manipulating licensed products and to highlight the information that would be useful to inform practitioners on the appropriateness of these manipulations.

## 2 Splitting tablets into segments

From a practical point of view this seems a simple operation where the tablets are scored to facilitate such a manipulation. It relies on the assumption that the active substance will be uniformly distributed throughout the volume of the tablet. However, the potential for dosage error is more apparent with small tablets and low dosage tablets (i.e. potent drugs where the active content may be in the sub-milligram range), and increases if the tablets are not scored. Devices for containing and cutting tablets are available and may be used in healthcare or domiciliary settings.

Some tablets should not be manipulated in this way, for example, enteric coated tablets, layered tablets (the matrix is not homogeneous) and many modified-release dosage forms; however it may be possible to manipulate some matrix forms (See Section 8).

**The manufacturer may consider providing information that would guide the dispensing pharmacist on the issues surrounding cutting tablets into smaller segments.**

## 3 Crushing tablets

The objective here is to reduce the monolithic tablet to a fine powder in which the active substance is assumed to be uniformly distributed, and which is amenable to dose reduction or to mixing in food or drink to facilitate ingestion. In the simplest situation a mortar and pestle might be used. A division of the powder might even be made by visual inspection in a domiciliary environment (obviously associated with a high risk of dosage error), or by weight, in proportion to the intended dose to be given. There is also the added risk of segregation of the active substance in the bulk powder caused by prolonged handling and vibration. In a hospital pharmacy environment, manipulations that may increase the homogeneity of the resulting 'bulk' powder might be as follows:

Milling of the tablets in a small laboratory hammer mill. Changes in particle size may influence bioavailability. Temperature rises may increase potential for chemical degradation or solid-state transitions, particularly in the case of steroids

An added manipulation which frequently used in the hospital environment is the blending of powdered tablets with a lactose diluent, subsequently filled into powder papers (sachets) or hard gelatin capsules by hand or using a hand-filling machine to facilitate the preparation of batches of up to100 or so. This manipulation requires technical skill in validation and operation.

There is a danger that blending with lactose may be applied as a default operation when this is not relevant. For example, active substances which are primary amines (e.g. amlodipine) are more appropriately formulated to avoid lactose because of the well-known interaction and instability in the presence of such reducing sugars.

There is also the risk that modified release tablets may be inadvertently crushed or manipulated in this way, so that their special advantageous properties are lost.

**The manufacturer may consider providing any available information on the suitability of tablets for crushing and on suitable powder diluents when pharmacists prepare capsules or powder sachets to allow administration of smaller doses. Any available information on the compatibility and stability of the crushed tablet with common foods and drinks (e.g. yoghurt, milk, water, fruit juices) and any known effects on bioavailability could be provided in the Summary of Product Characteristics.**

## 4 Opening capsules

This is a refinement on crushing tablets, in that the manufacturer has already established a powder matrix. As in the case of crushed tablets (see above), the capsule contents might be divided by visual inspection or weight with the attendant risks, or dispersed into drink/food to facilitate ingestion. Modified release preparations of coated particles packed in capsules can usually be opened and dispersed in food or drink. The contents of capsules may be manipulated into powder papers or smaller capsules as above.

**The manufacturer may consider providing examples of any known compatible/incompatible foods and drinks and commenting on any known effects on bioavailability.**

## 5 Dispersing tablets / capsules and taking proportions

A further manipulation of a powder prepared from tablets or taken from inside capsules, is to disperse it in a suitable suspending liquid and achieve dose reduction by volumetric means rather than gravimetrically or otherwise. There is a risk of dosage error arising from sedimentation or settling of the resulting dispersion, and this can be reduced somewhat by using a high viscosity suspending medium.

The risks here lie in the errors involved in volumetric measuring of viscous liquids and losses due to hydrolysis in aqueous media. In some cases, the active substance may dissolve from the powdered matrix and be taken into complete solution, and in these cases the error is reduced although losses due to hydrolysis reactions may be expected

**If available, manufacturers may consider providing information to enable extemporaneous preparation of oral liquids or suspensions from the authorised tablet or capsule dosage form.**
**Manufacturers may consider and provide any information on the suitability of tablet or capsule dispersion for the purposes of volumetric measurement to administer a proportion of the 'adult' dosage form.**

## 6 Cutting/covering transdermal patches

Since the dose delivered through the skin is proportional to the surface area of a transdermal patch in contact with it, it is theoretically feasible to halve the dose by halving the area of the patch, other things being equal. Therefore, there are many reports of caregivers cutting a patch with scissors in order to obtain a reduced paediatric dose in proportion to the reduced area. There are a number of risks with this particular manipulation.

- The most important problem is the different structure of the maturing skin in neonates. Despite manufacturers' claims that their transdermal products contain a specific 'release-controlling' membrane, it is likely that the main rate-controlling factor is the skin itself, the stratum corneum in particular. Therefore the absorption kinetics relating to adult transdermal patches should not be expected to apply to the younger members of the paediatric population.
- It may be difficult to decide what exactly is the area of the patch – the area of the matrix may be less than the area presented to the eye and asymmetric cutting can introduce errors.

- The matrix of the patch is hermetically sealed in the adult form. Cutting exposes the cut edges to the atmosphere and possible mechanical erosion and oxidative degradation
- Cutting is contraindicated in gel-filled patches

**Manufacturers may consider providing any available information on the effect of cutting a patch or covering a proportion of the patch, on the release characteristics of the active substance.**

## 7 Cutting suppositories

Again, this assumes a uniform distribution of the active substance in the suppository matrix.
Accurate adjustment of dosage is difficult in this case, since very few suppositories are presented in a convenient shape facilitating halving by simple visual inspection. Cutting along a plane of symmetry (i.e. vertically rather than horizontally) would be an obvious solution and carries less risk of dosage error but the resulting shape may not be optimal for rectal insertion. Horizontal truncation of an asymmetric or bullet shape or rounded truncated cone carries the highest risk of dose error

**Manufacturers may consider providing any available information on uniformity of dispersion of the active substance in the suppository.**

## 8 Injectable solutions administered by other routes

Using injections for oral administration is expensive, but in general this manipulation has the least potential for dosage error since many injections are dilute aqueous solutions, non-viscous, and a dosage reduction can be obtained if necessary with a small syringe, possibly after further dilution. Powders for injection may be taken up in a suitable diluent in the normal way, prior to dose reduction.
For oral administration, unpleasant taste could be a problem and will have to be considered unless nasogastric tubes are used. However, there are a number of more significant risks.

In the case of preserved or multidose injections these may contain benzyl alcohol, propylene glycol, or other substances, or have a pH or osmolality potentially harmful to neonates or children (see Section 4).

Also, the stability of injection solutions may be compromised on dilution, and in the absence of reliable technical information from the original manufacturer, it should not be assumed that the stability profile of the original product will be duplicated on dilution.

Injections have sometimes been given by the pulmonary route following nebulisation. Ignorance of the precise composition of the parent (adult) formulation could pose a significant safety risk in the case of injections stabilised with sulphite-based antioxidants which may provoke bronchoconstriction.

**Manufacturers may consider providing information on request that will allow the pharmacist to determine the suitability of an injection solution for administration by other routes.**

## ANNEX 2

## Methods to assess the taste of a medication

### 1. Quantitative evaluation of the taste on the basis of analytical methods

The analytical method utilized is very similar to that for determination of the drug release and is mainly based on the detection of drug substance within a short period of time in aqueous medium (e.g. artificial saliva). It is regarded as an indirect method for assessing taste masking since it does not contribute in the evaluation of taste and sweetness of the drug product. It is commonly used for measuring the effectiveness of coating and complexation within formulation. Taste masking is achieved, when in the frame of 1-2 min drug substance is either not detected or the detected amount is below the threshold for identifying its bad taste.

### 2 Quantitative evaluation of the taste using a taste sensor

The taste sensor (electronic tongue, e-tongue) can detect taste in a manner similar to human gustatory sensation. Taste substances cause changes in electric charge density of the lipid/polymer membrane surface and / or ion distribution near the surface of the membrane of the sensor. The total electric change is given as the response membrane electric potential for the substance tested. The response electric potential is different for substances possessing different taste qualities in each membrane and differs from one membrane to the other. Thus, taste information is acquired as a pattern of membrane potentials (3).
The output of the electronic tongue is the taste quality of the formulations tested and their intensity compared either to established standards (e.g. assessment of bitterness using quinine hydrochloride or caffeine solution at different concentration levels) or other references (e.g. the formulation containing the active compound to be tested without any tasting masking agents).
The methodology may be applicable to many paediatric dosage forms (1,2). The procedure is comparatively inexpensive and easy to conduct. In addition to taste evaluation during drug product development, taste sensors would also be useful in screening new substances for bitterness and monitoring the stability of taste over time.

### 3 Qualitative evaluation of the taste by a taste panel

Consumer testing is acknowledged as the best population to assess a product. Consumers are regarded as individuals who are pre-screened to be actual users of the product tested with particular interest to product quality. In line with this definition and taking into consideration the sensory differences between adults and children, it is evident that the children as a target population are regarded as the most suitable panel for taste assessment of paediatric formulations.

#### 3.1 Recommendations for performing taste trials in children

To design a palatability study in children the following parameters need to be considered as key elements:

- The test should be short in order to match children's attention span
- As children are easily distracted, the test has to be intrinsically motivating and "fun" to do.
- The procedure has to be as easy as possible so that even very young children (e.g. pre-schoolers) could understand it.
- In order to ensure reliable assessment preventing confusion by the children and taste fatigue, the number of variants to be tested should be limited to a maximum of four.

Palatability studies are not described in any regulatory guidance but must be considered as clinical studies performed by qualified personnel with Ethical Committee approval and informed consent from

parents or guardians and assent from the child as appropriate. There may be ethical difficulties in designing suitable safe studies in which children can easily participate

### 3.2 Participation and test performance

Generally, children aged 4 years and older are considered to be able to participate in taste trials. Younger children are very often shy and reluctant. Furthermore, their ability to understand and follow the guidance is sometimes limited; they also loose their interest or have difficulty concentrating during the entire testing period. The failure rate varies up to 50 % depending on the design and duration of the test. In addition, they are often unable to communicate their feeling and preferences (1,2).
In order to increase children's understanding and motivation it is recommended to start off with either high concentrations of the testing agent to be assessed (flavour or sweetener) or with known compounds (e.g. commonly used flavours) followed by the more specific, unusual one (e.g. strawberry or cherry followed by passion fruit). In some cases to begin the test with high concentrations of testing agent (e.g. sweetener) would be inappropriate due to the unpleasant sweet taste or the bitter aftertaste. Procedures to remove the previous taste may include repeated rinsing of the mouth, eating of salty crackers and a sufficiently long interval between sessions.

### 3.3 Sensory evaluation: affective and analytical testing, and ranking

Probably the most critical item in sensory evaluation is defining the objective i.e. what exactly should be determined. The test objective will determine the type and age of subjects and the methodology to design, conduct and interpret the study and its outcome (4).

- Affective testing includes acceptance / preference testing. Typical questions addressed are "which sample do you prefer", "how much do you like it", and "what don't you like".
- Analytical testing requires the use of objective sensory methodologies aiming to determine the characteristics / properties of the test item, without defining acceptance / preference measures. Analytical testing answers questions such as "which sample is more bitter" or "which sample is different". Analytical methods help define the sensory properties of the medicinal product preparation and differentiate between variants, but will not directly predict how much a variant will be liked. It is often used as a technical tool to support development / optimization purposes.
- Ranking is a very straightforward method that can be used for preference or analytical assessment ("please rank samples in order of your personal preference" or "please rank samples in increasing order of bitterness", respectively). The advantage of this method is its simple procedure. However, the study results may be biased due to limited memory and attention of the tester during the entire testing period. This limitation may be more pronounced depending on the age of the subjects participating.

### 3.4 Evaluation principles

In most cases smell, texture, taste and aftertaste, and sometimes also appearance (e.g. if coloured) are addressed. The language used in the questionnaire has to be simple, intelligible and plain for all participants independent of their age, social and developmental level. It is recommended to utilise commonly used terms relevant to the age of the participants to describe these properties:

- sweet, salty, sour, and bitter characterizing the taste
- thin, thick, viscous, gritty aiming to portray the texture of the testing item
- sweet, salty, sour, and bitter but also astringent, numbness, or freshness for the aftertaste

The following two principles for taste evaluation are established in palatability studies with children: verbal judgment and facial hedonic scale (3).

- Verbal judgement followed by scoring in a scale of e.g. 1 to 5 (score 1 corresponds to very good and score 5 to very bad) facilitates the statistical evaluation of the data obtained (5)
- While the facial hedonic scale allows the expression of preferences using a pictorial scale.

Children below 5-6 years are not considered to be able to express differences in taste perception by use of the preferential method. A reliable estimation of differences particularly in this age group (< 5 years) might be achieved using the child's own spontaneous verbal judgements following a control question. The facial hedonic scale can not be used solely to discriminate between the tastes of tested formulations in the lowest age group. Young children may link the figures with things other than taste (e.g. happy face = I will not stay longer in hospital, sad face = pain or discomfort). Facial expressions and behaviour pattern of the subject itself (wry faces, shrug shoulders, vomit or spit the formulation out) may also reflect the acceptance of the tested formulation (1,2).

In order to assure reliable outcome of a palatability study with young children it is suggested to involve parents, guardians or health providers in the study, asking about any discomfort or other observations in relation to the acceptance of the study medication.

Since older children judge more critically than younger ones, they are able to discriminate between the formulations using both the verbal judgement and hedonic scale.

Independent of the age of the children and the evaluation principle selected, it is suggested to include in the questionnaire concluding questions to the overall taste evaluation of the formulation such as "which formulation was the best" or "which formulation tasted worst". Similar approaches may be followed for the assessment of the flavour used: "which of the tested flavours did you like the most" or "which one did you dislike the most".

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**ANNEX 1**

**ANNEX 2**
**(see also references and bibliography under Section 5 )**