

# Annex 2

## FIP–WHO technical guidelines: Points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products

<b>1. Introduction and scope</b>	89
1.1 Background	89
1.2 Purpose	90
1.3 Target audience and health-care settings	90
<b>2. Glossary</b>	90
<b>3. Alternatives to compounding</b>	92
3.1 Sourcing of a commercially-available (marketed) or manufactured product if available	92
3.2 Dose rounding	93
3.3 Therapeutic alternatives	93
3.4 Manipulation of dosage forms	93
3.4.1 Tablet splitting	94
3.4.2 Tablet/capsule dispersion for oral administration	94
3.4.3 Crushing tablets/opening capsules and mixing powder with food or drink	95
3.4.4 Giving the injectable form by the oral route	96
3.4.5 Splitting suppositories	96
3.4.6 Rectal administration	97
3.4.7 General advice when changing the route of administration	97
<b>4. Compounding</b>	97
4.1 Good manufacturing practices aspects	97
4.2 Some potential problems	98
4.2.1 Oral liquids	99
4.2.2 Microbial contamination	100
4.3 Basic considerations	100
<b>5. Information, availability and access</b>	106
5.1 Standards of practice and guidelines	106
5.2 Formularies and compendia	106
5.3 Source and supply	106
5.4 Networks and information services	107
<b>References</b>	107
<b>Appendix 1</b> Examples of therapeutic alternatives to extemporaneous formulations	109

# 1. Introduction and scope

## 1.1 Background

Paediatric patients should have access to authorized, age-appropriate preparations of medicines that can be administered safely and effectively. Nothing in this document should detract from this objective. However, it is recognized that such preparations are not always available and in such cases a safe and effective alternative must be sought.

In the context of paediatric pharmacy practice, and for the purpose of this document, compounding is the technique applied by pharmacists to produce medicines from active pharmaceutical ingredients (APIs) or using authorized medicines when no commercially available, authorized, age-appropriate or adequate dosage form exists. Unless stated explicitly in this document, the compounded medicine is assumed to be dispensed immediately after preparation and not kept in stock. Compounding does not apply to reconstitution of authorized medicines prior to dispensing. A clarification of the terminology of preparation of medicines for children has been proposed by Ernest et al. 2012 (1).

The risks and benefits of compounding and of the alternatives should be fully understood by practitioners. Practitioners who do not have appropriate knowledge should seek advice.

Compared to the use of authorized medicines there are significant risks associated with compounding; quality, safety and efficacy can rarely all be assured, and many errors have been reported in the preparation of such medicines. In some situations compounding of a medicine for a child may be the only option, which may be supported by evidence of quality and occasionally evidence of bioavailability by industry or other parties, such as academia. There may be alternatives to compounding, which should also be considered, for example, use of a commercially available therapeutic alternative or manipulation of authorized dosage forms.

This points-to-consider document is supported by a literature review of the evidence available (2). An annex to the report contains an update on the abstracts and papers published in 2010–2015.

This document is to be considered as a time-limited document that addresses current needs for advice in the search for an alternative to an authorized, age-appropriate dosage form. Wherever possible the guidance is informed by the relevant evidence. However, the evidence base is weak or non-existent in most situations. Consequently, the guidance is predominantly informed by best practice, based on sound scientific and therapeutic principles and expert consensus. Although the guidance takes the form of a working practical document it is important to invite comment and input from interested practitioners so that the guidance can be developed further in response to feedback. The document

addresses mainly paediatric medicines for oral administration; comments and proposals concerning other routes of administration are invited as well.

## 1.2 Purpose

The purpose of the document is to:

- provide evidence-based or best practice advice about alternatives to compounding of medicines for paediatric patients;
- describe the main potential problems of compounding and educate practitioners on how to avoid them;
- provide brief advice on compounding;
- reduce the risk of providing children-specific preparations without informed knowledge.

The document will not reproduce guidance and standards that already exist (e.g. good manufacturing practices (GMP) standards for facilities and documentation). Where appropriate, reference is made to the relevant resources and publications.

## 1.3 Target audience and health-care settings

The document is intended for a wide audience of health-care stakeholders including:

- all practitioners involved in health care of the paediatric population but mainly pharmacists, physicians, paediatricians and nursing staff;
- national medicines regulatory authorities and professional bodies, e.g. national paediatric organizations and national pharmacy associations;
- general hospitals and health clinics;
- specialized paediatric hospitals and primary care clinics;
- the pharmaceutical industry, given its role in providing information.

Pharmaceutical manufacturers can often provide useful information on validated compounded formulas and other information relating to the manipulations and specific characteristics of formulations.

## 2. Glossary

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

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

**authorized dosage form.** A pharmaceutical dosage form that has been authorized by the competent authority to be marketed for the treatment of specific indications.

**beyond-use date.** The date after which a compounded preparation should not be stored, transported or used; the date is determined from the date or time the preparation is compounded. It is also known as the *expiry date*.

**compounding.** Preparation under the supervision of a pharmacist following national legislation of an unlicensed medicine to meet the specific needs of a patient when no suitable authorized dosage form is available. This may involve preparation from the authorized dosage form or from the active pharmaceutical ingredient and usually involves addition of excipients to produce an acceptable product.

**dispensing pharmacy.** The pharmacy receiving the prescription for a patient and providing the pharmaceutical preparation to the patient. For compounded medicines, the dispensing pharmacy is not necessarily the compounding pharmacy.

**dose rounding.** Amending a dose that has been calculated accurately on the basis of body weight or surface area to correspond with an amount of the dosage form that is easy to measure and administer. Account of therapeutic index should be taken before rounding the dose.

**excipient.** A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture or compounding of a pharmaceutical product.

**expiry date.** The date after which a compounded preparation should not be stored, transported or used; the date is determined from the date or time the preparation is compounded. It is also known as *beyond-use date*.

**good manufacturing practices.** A system of practice and processes to assure the quality and safety of manufactured pharmaceutical products, specified in, for example, WHO guidelines.

**labelling information.** Information to the user provided on the container or package label or in the patient information leaflet.

**manipulation of a dosage form.** Authorized dosage forms may be manipulated (or modified), often at the point of administration, to provide the appropriate dose (e.g. by segmenting tablets) or to facilitate administration (e.g. by crushing a tablet and adding to food).

**pharmaceutical dosage form.** The physical form in which a medicine is presented; the name of a dosage form combines its physical form and the intended route of administration, e.g. a tablet (to be swallowed), oral suspension (liquid suspension of solid particles intended for oral intake and swallowing).

**route of administration.** The way in which a medicine is given to a patient, e.g. oral administration (administration via the oral route), rectal administration (administration to the rectum), parenteral administration (administration via the blood, muscular or subcutaneous routes).

**summary of product characteristics.** Summary of product characteristics approved by the competent authority. The information may alternatively be presented in the container or package label.

**verification.** A process of providing any type of adequate evidence, e.g. new (bio)analytical data, from the literature or by referencing to existing practices to support that the proposed modification will not change the pharmaceutical characteristics of the original preparation in a way that will negatively impact the safety and/or efficacy of the medicine.

### 3. Alternatives to compounding

Before deciding to compound, consider possible alternatives that will give the greatest assurance of clinical effectiveness and safety.

The main alternatives to compounding are described below.

#### 3.1 Sourcing of a commercially-available (marketed) or manufactured product<sup>1</sup> if available

A marketed, authorized, age-appropriate finished pharmaceutical preparation should always be sourced when available. Where appropriate and in accordance with the national regulations, this could include:

- off-label use of a medicine authorized in the country where the medicine is to be dispensed;
- (off-label) use of an imported product authorized in the country of origin;
- use of a manufactured product made in authorized facilities in the country where the medicine is to be dispensed.

<sup>1</sup> This includes products prepared to GMP standards, for example, at an accredited hospital manufacturing unit.

The logistics of supply, costs and access are obvious factors that might present obstacles, but practitioners should liaise with suppliers, importers and regulatory authorities to access these products if possible.

Importation of products may be expensive, and reputable suppliers should be used to avoid spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines. Quality assurance systems should be in place, for example, to ensure that recall systems are available and that information is provided in the local language.

The use of compounded products for children should not be justified on the grounds that they are cheaper than marketed products. Other options, including local manufacture in accordance with GMP standards, should be investigated.

### 3.2 Dose rounding

If the dose prescribed does not correspond to a dosage form that is commercially available, consider whether the dose can be suitably amended while maintaining safety and efficacy.

The therapeutic index of the medicine and patient characteristics need to be considered before making a decision.

Some medicine doses are calculated accurately on the basis of body weight, yet the therapeutic index is such that one dose can be used for a broad age and weight band. Consult the WHO Model formulary for children.<sup>2</sup>

### 3.3 Therapeutic alternatives

If a medicine is prescribed in a formulation that is not available, e.g. in an age-appropriate form, consider the possibility of using a commercially available medicine with a similar therapeutic action, which is available in a more suitable form. Examples are presented in Appendix 1.

### 3.4 Manipulation of dosage forms

In situations where the prescribed dose is different from what is marketed, or there are administration-related difficulties, the possibilities for manipulation of a dosage form as outlined below can be considered. Formularies or manufacturer's information, if available, and the labelling or the summary of product characteristics (SmPC) should be consulted.

A report with evidence-based guidelines on the manipulation of medicines to obtain the required dose for children was published by the

<sup>2</sup> Available from: <http://apps.who.int/medicinedocs/en/m/abstract/Js17151e/>.

Manipulation of Drugs Required in Children (MODRIC) research group in 2013 (3).

The practitioner should bear in mind that manipulation, such as tablet splitting, tablet/capsule dispersion, or tablet crushing and mixing with food or drink, may increase the potential for inaccurate dosing and may affect the efficacy, stability and bioavailability of the dosage form, in particular when mixed with food or drink. Excipients that are safe for adults may not necessarily be so for children.

When medicines are mixed with food or drink, including breast milk for very young children, an unpleasant tasting mixture may cause aversion in the child. In addition, the compatibility of the product with the food, drink or breast milk will need to be taken into account. Where a child shows signs of refusal or aversion other options should be considered.

#### 3.4.1 **Tablet splitting**

Not all tablets should be split. In general, those with a sustained-release or enteric coating should not be split, but it may be possible to split tablets with a sustained-release matrix. Formularies or manufacturer's information, if available, and the product label or SmPC should be consulted.

Some tablets allow splitting, either by breaking, if scored, or by using a tablet cutter designed for the purpose. If the child is able to take solid dosage forms safely, a tablet segment can be given; otherwise it can be dispersed or mixed with food or drink as described below in section 3.4.3.

Tablets without a score line cannot, in general, be split into uniform segments meeting relevant uniformity requirements. Information about possible splitting of such tablets may however be provided in the SmPC or on the label. Tablet splitting was reviewed by Freeman et al. (2012) (4).

Consider on a case-by-case basis whether splitting of tablets might lead to toxicity or reduced effect as a result of inaccurate dosing or an effect on the release profile. This is especially important in situations where the API is potent or has a narrow therapeutic index, if there is a lack of appropriate information, or if an accurate dose cannot be assured.

Consideration should be given to splitting tablets with an appropriate commercial tablet splitter in the pharmacy. If possible, tablets with score lines and uniform distribution of the API should be sourced and information sought on the stability of segments. If carers are cutting segments, they should be given a suitable tablet splitter and receive adequate instruction on the method for preparing and storing tablet segments.

#### 3.4.2 **Tablet/capsule dispersion for oral administration**

It may be possible to disperse immediate-release tablets or the contents of capsules in water or another liquid. If the tablet disperses, the tablet or a fraction

of it can be dispersed in a small volume appropriate for the child concerned and the whole dose given when a suspension is formed, or mixed with a flavoured vehicle if required. To ensure that the whole dose is administered the measuring device should be rinsed and the resulting solution or suspension administered. It is necessary to consider the impact of dispersion and the risk of interactions with the vehicle on the bioavailability.

Conventional tablets do not disperse readily but some form a suspension within a short time. Soluble tablets and dispersible tablets disintegrate and dissolve or disperse within a short time in water at room temperature.

If the tablet disperses in a known volume of water to form a stable suspension, a fractional dose can be appropriately measured with a syringe. As extraction of soluble API from the tablet may be incomplete, the suspension should be shaken or stirred before measuring the dose and not filtered unless it has been established that the API is fully dissolved. Dose uniformity of the prepared suspension cannot be assured and the risk of overdosing or underdosing must be considered. This may depend on the volume of prepared suspension that is to be extracted for administration. Any such tablet (whether a dispersible or conventional-release tablet) compounded to a dispersion or solution should be administered immediately after preparation and the remainder should be discarded.

When the dispersion is intended for tube feeding, parameters such as particle size, viscosity, dosing volume and compatibility of the oral preparation with the tube material should be considered. Dispersions may be too viscous or may contain large particles that can mean that administration by feeding tube is not feasible. Adsorption of API to the tube material results in inappropriate dosing; this concern is most relevant for lipophilic and low-dose potent APIs.

WHO is promoting the use of flexible solid oral dosage forms such as dispersible tablets (5). Custom-made dispersible tablets for paediatric dosing should be used wherever possible but it is still necessary to ensure that carers understand how they are to be administered.

### 3.4.3 **Crushing tablets/opening capsules and mixing powder with food or drink**

The practice of crushing tablets or opening capsules and adding the powder to a palatable drink or sprinkling it onto solid food has been reviewed (6). Although common, there may be little evidence to support the efficacy and safety of this practice since stability and bioavailability may be altered. With the exception of multiple-unit preparations, which can be opened and administered without affecting efficacy and safety, modified-release tablets and capsules cannot be crushed or opened without affecting bioavailability and/or stability, and this should therefore not be done. Insoluble tablet excipients are in suspension and

may compromise product appearance, whereas soluble excipients may alter stability, for example, by changing the pH of the preparation.

In the case of potent APIs, consider the risks associated with handling of powdered material to parents or carers.

In general, the decision on whether to crush tablets should be based on bioavailability and acceptability studies. Information should be sought from manufacturers (e.g. the label or SmPC and website) and formularies whenever possible. The process is acceptable only if bioavailability is not affected by food or drink, and the product has to be used immediately to minimize stability problems.

It is difficult to ensure that a complete dose has been taken and the practice of nurses and carers handling powdered medicines may present health concerns. Tablet dispersion may be a simpler, more reliable and potentially safer method.

Liquid-filled capsules should generally not be opened since it is difficult to remove and measure the total contents.

#### 3.4.4 Giving the injectable form by the oral route

Oral administration is possible for some injections. If the injectable form of the API is the same as the oral form (for example, labetalol hydrochloride, ondansetron hydrochloride) it can be assumed that the API will be absorbed enterally from the injectable formulation. However, as the API is in solution, more rapid absorption and higher peak levels may occur than would result from the slower absorption from a solid oral dosage form. When evaluating whether an injection is suitable for oral use, specialist advice, e.g. consultation with a medicines information centre in the region, should be sought because there are important factors which must be considered, e.g. first-pass effect, oral bioavailability, gastric acidity (e.g. effect on stability), pH effects (e.g. precipitation of soluble salts of weak acids) and palatability.

Injections may contain excipients that may have undesirable effects in some patients, e.g. propylene glycol and ethanol. The pH of some injections may be high or low and they should therefore not be given orally, or alternatively should be diluted before administration to avoid irritation. The taste of the injectable form may not be known and may not be acceptable. Advice should be sought from the manufacturer and from experts to assist in deciding whether the injectable form can be administered orally.

#### 3.4.5 Splitting suppositories

There is little information available on the accuracy with which suppositories can be split. Splitting is usually associated with major problems with regard to accurate dosing and is therefore generally discouraged. Most commercially available suppositories are formulated as suspensions, which means that

sedimentation of the solid API particles may occur during solidification of the suppository; therefore, if suppositories need to be split, this should be done lengthwise.

Therapeutic index and the consequences of over- or underdosing should be taken into account when determining whether it is safe to split suppositories. If possible, this should be done in the pharmacy.

#### 3.4.6 Rectal administration

There may be opportunities to give oral or injectable dosage forms by rectal administration (7).

#### 3.4.7 General advice when changing the route of administration

Whenever a change of the route of administration for an authorized medicine is considered, advice should be sought from formularies and the literature and even from specialists. In general, altering the route of administration results in a different pharmacokinetic profile introducing a high risk of dosing errors and may compromise safety and efficacy. Hence, this practice is generally discouraged.

## 4. Compounding

### 4.1 Good manufacturing practices aspects

The dispensing pharmacy receives the prescription for a patient and provides the pharmaceutical preparation to the patient. For compounded medicines the dispensing pharmacy is not necessarily the compounding pharmacy. Regardless of where the product is compounded the dispensing pharmacy is responsible for ensuring the safety and quality of the product.

When a batch of non-authorized medicine is prepared, including for stock, the preparing pharmacy or hospital unit should meet – depending on a risk assessment – the GMP or good pharmacopoeial practices (GPhP) requirements pertaining to personnel, premises and equipment, quality assurance system, documentation and product dossier. Further, an authorization by the competent authority to carry out operations may be needed, in accordance with the national legislation. In this respect, one should refer to the relevant international and national guidance and to other guidelines, including WHO guidelines on GMP (8, 9), the Pharmaceutical Inspection Co-operation Scheme (PIC/S) *GPP Guide to good practices for the preparation of medicinal products in healthcare establishments* (10) and corresponding national guidelines.

When compounding is a one-off event, the intended prescription should be prepared for an identified individual patient for immediate dispensing. In such cases requirements may be less strict. Nevertheless, certain requirements need to be met:

- the preparing pharmacy should have appropriate premises and equipment;
- the pharmacist and staff, or entitled persons, must have sufficient training and background for compounding;
- access to relevant literature (e.g. pharmacopoeias, formularies, handbooks and scientific journals) and the Internet must be available;
- general instructions for the preparation of each dosage form should be available;
- a record on each preparation should be retained showing the calculations, key processing and packaging steps, and also including the name of the person responsible for each step.

#### 4.2 Some potential problems

In some situations, for example, if the method of preparation and the stability of an oral liquid are well documented, e.g. if compounding has been supported by evidence of quality, stability data and occasionally evidence of bioavailability by industry or other parties, such as academia, and all facilities and ingredients are available, it may be less pressing to seek an alternative to compounding. On the other hand, if there are no stability data and, for example, the API forms a caking suspension in the only available excipients (e.g. a syrup), an alternative must be considered to ensure safe and effective treatment.

In any case, the decision on how to prepare and/or provide an unlicensed preparation should be based on an assessment of risks and benefits of the dosing strategy. On a case-by-case basis, potential benefits from their use should be weighed against all possible risks arising from preparation and administration of such medicines. Even in cases where the compounded preparation can be considered a verified formulation, the impact of compounding on bioavailability may not be known.

Formulation of a compounded medicine is associated with a number of potential problems that may impact on its safety and effectiveness. Awareness of the relative complexity of the formulation and of the things that can go wrong will help to avoid such problems. Guidance on compounding has been published (e.g. 11). A review of extemporaneous compounding is also available (12).

Consideration must be given to the properties of the API (e.g. aqueous solubility, pH effect on solubility, particle size, polymorphism) and stability of both API and the compounded formulation, i.e. chemical, physical and microbiological instability.

Care must also be taken in the selection of excipients and their safety in relation to the age of the child as well as any possible adverse effects of the

“inactive” components of the preparation should be considered. The use of preservatives, ethanol and sugars must be carefully considered. Some guidance and literature references on the formulation can be found in *Development of paediatric medicines: points to consider in formulation* (5).

#### 4.2.1 Oral liquids

Deterioration of an oral liquid may be a result of chemical, physical or microbiological instability which can lead to a subtherapeutic dose of the medicine, exposure to toxic degradation products or ingestion of unacceptable numbers of microorganisms. It is important for pharmacists, clinicians and nursing staff to be aware of potential problems caused by instability and microbial contamination to ensure that any medicine used is effective and safe.

APIs in compounded liquids may be susceptible to chemical reactions leading to degradation. Publications reporting the stability of compounded paediatric preparations include a review by Glass and Haywood 2013 (13). The most common reactions are *hydrolysis*, oxidation and reduction. Usually the reaction rate or type is influenced by pH. Other factors that may increase the rate of reaction include the presence of trace metals which catalyse the oxidation of captopril, methyldopa or exposure to light, which catalyses the oxidative degradation of 6-mercaptopurine. The rate of chemical degradation usually increases with temperature.

The API in the preparation may be totally or partially in solution or predominantly in the solid state as a suspension. APIs in solution are more susceptible to chemical degradation than APIs in the solid state (i.e. suspensions); thus suspensions of acetazolamide and chlorothiazide are more stable than solutions. However, it cannot be assumed that a compounded suspension is always more stable than a solution. In a suspension, an equilibrium exists between the API in the solid state and an API in solution, and even though the amount of API dissolved may be minimal, the conditions could be optimal for degradation. Furosemide is a notable example: it undergoes hydrolysis in acidic conditions where the solid state is predominant, but is much more stable at alkaline pH where it is totally in solution.

Preparations made from tablets contain excipients such as binders and disintegrating agents in addition to the API. These excipients may reduce chemical stability by changing the pH to a value at which more rapid degradation occurs. This probably explains why amiloride solution prepared from pure API is more stable than an oral liquid prepared from tablets.

Hygroscopicity and/or moisture-sensitivity of the API also play a key role in degradation. These characteristics of the API(s) should be understood before compounding from a tablet to a liquid form. A common example of such an API is tenofovir disoproxil fumarate.

Dispersions and suspensions of medicine with low therapeutic index require special consideration with regard to efficient resuspension to avoid medication error.

#### 4.2.2 Microbial contamination

Microbial growth in an oral liquid may cause a foul odour and turbidity and adversely affect palatability and appearance. High titres of microorganisms may be hazardous to health especially in very young or immunocompromised patients. By-products of microbial metabolism may cause a change in the pH of the preparation and reduce the chemical stability or solubility of the API. Microbial contamination during preparation must be minimized by using clean equipment, water of adequate quality and by avoiding contaminated raw materials and containers. If sodium benzoate or benzoic acid are used as antimicrobial preservatives, the final pH must be less than 5 so that the active unionized form is predominant. Consequently the API must also be stable at this pH.

Many factors can reduce the effectiveness of the preservative, including use of contaminated materials, chemical degradation, binding of preservative to suspending agents or tablet excipients, incorrect storage or unhygienic use of the final product.

#### 4.3 Basic considerations

- *Quality of API and excipients*

It is important to ensure that the API and the excipients meet pharmacopoeial standards with regard to both identity and purity. The choice of excipients should be restricted to those that have been used in authorized medicines intended for the same route of administration and at similar concentrations.

- *Consider use of an authorized dosage form as a starting point*

It may be safer and more effective to crush tablets or use the contents of hard capsules with an appropriate suspending vehicle than to prepare medicines from an API and excipients. There are many formulations available with a validated shelf life but sourcing of suspending agents may be difficult and/or expensive.

There might be instances when a pharmacist crushes a number of tablets or opens a number of capsules, dilutes the powder with a suitable excipient and doses the powder in ready-to-use single-dose sachets. Before doing so, consider the stability of the preparation, including stability with respect to humidity and exposure to air.

- *Consult literature and guidelines if available*

Use a validated formulation whenever possible (i.e. based on literature, stability studies and guidelines). Consult product information and the latest national and international guidelines and/or a specialist information centre if possible.

- *Potential medication error*

Medication errors in preparing compounded medicines occur often, and some have resulted in serious harm to patients or even in death. The potential for medication error must be recognized and steps taken to minimize the risk. As a minimum, this will include the use of a worksheet listing the formulation ingredients and the identity of the ingredients; quantities, calculations and measurements should be double-checked by trained personnel and signatures provided. The pharmacist responsible should check the final product and label against the signed worksheet, ingredients and prescription.

- *Exercise caution in extrapolating from other formulations*

Caution is required when extrapolating the formulation from a published study or formulary. Formulations made from APIs may be more stable than formulations made from solid dose forms and vice versa. Tablet and capsule excipients can increase or decrease the stability of the API in an oral liquid preparation. The salt form of the API used in a published study could be different to the form locally available and this may affect its solubility, bioavailability and stability. Consult publications and pharmacopoeias, and seek specialist advice, if possible.

Similarly, the results of a published study using an API mixed with a commercial suspending base cannot generally be extrapolated to a situation where the same API is mixed with a simple base of syrup or glycerol.

Formulations for compounded medicines based on APIs and crushed tablets are not interchangeable.

- *Dose uniformity may be a problem – explain the importance of shaking prior to use*

If the API is poorly soluble in water, uniformity of dosing may be a problem and a suspending agent will be required. Always check that the finished preparation resuspends under in-use conditions and explain the importance of resuspension by shaking to patients or their carers.

As excipients and other formulation components can affect solubility, all compounded liquid formulations should be shaken prior to administration. Some of the API may not be in solution even if it is highly soluble in water. The only exception would be if the preparation is made from pure API and it can be assured that the entire API is in solution.

Suppositories have sometimes been melted and recast into smaller moulds. This option is associated with a risk of recrystallization and of affecting the distribution and solubility of the API, resulting in over- or underdosing. Further, re-melting may affect degradant levels. Re-melting is therefore generally discouraged.

- *Exceptionally, when no published formulation is available*

When no published formulation is available the pharmacist must assess the risks associated with the different options and use his or her knowledge and experience to formulate a product taking into account the need to:

- obtain information on the physicochemical properties of the API if available.

If possible, obtain basic physicochemical information about the API, especially its aqueous solubility at the expected pH of the final preparation. This allows a judgement to be made as to whether an API solution or suspension is formed at a particular dose-relevant concentration.

- test the physical characteristics before using the preparation to treat a patient.

FPPs of the same medicine may vary worldwide, especially with respect to the content of excipients. Such differences can influence the safety, efficacy and acceptability of the preparation. Basic performance tests should be done before the preparation is used in a patient, particularly on formulations prepared for the first time. Tests include ease of resuspension and pouring, degree of caking on storage, and observation of physical behaviour and characteristics.

- consider risk of microbial growth.

All compounded liquid formulations are highly susceptible to microbial growth. Oral liquids that are not adequately preserved will support rapid growth of bacteria and fungi especially at warm to hot temperatures and can pose hazards to patients especially

those who are immunosuppressed. An antimicrobial preservative should be included if the final product is likely to be used beyond 2–3 days, even when it is stored under refrigeration.

The effects of the addition of the preservative on interactions between pH, stability and effectiveness of the preservative should be carefully taken into account.

Compounded liquids should be prepared under conditions that minimize the introduction of microbial contaminants.

- *Use appropriate final containers*

Final containers and closures should be clean and free from dust and other residues. Use of new containers is recommended. Containers that are reused should be thoroughly washed, rinsed with sterile or freshly boiled water and dried. Light-protective (e.g. dark plastic or amber glass) containers should generally be used.

Consider the use of a light-protective wrapping such as foil if a light-protective container is not available. When selecting the final container, consider the interactions between the container and the product, for example, the possibility of adsorption to plastic containers.

- *Dosing device*

For liquid preparations, the feasibility of appropriate dosing should be confirmed bearing in mind that not all dosing devices may allow delivery of the required volume. Most compounded liquids should be shaken prior to administration and this may introduce entrapped air in the liquid, which could cause problems with accurate measurement of small volumes.

- *Consider in-use storage*

In-use storage conditions may vary considerably from those in a published study or formulary recommendation. Always consider whether it will be possible to store and use the preparation under the optimal conditions described in the study; usually refrigeration, protection from light and minimal possibility of in-use contamination. If these conditions are not possible locally it can be assumed that the preparation will be less stable and more susceptible to microbial growth. Reduce the shelf life according to professional judgement. If possible, obtain expert advice.

- *Expiry date*

It is recommended that each compounded preparation be given an expiry date assigned in a conservative way and taking into account

API-specific and general stability documentation and relevant literature when available.

When an authorized medicine is used as the source of the API, stability information can be obtained from the manufacturer. Otherwise, applicable information on stability, compatibility and degradation of ingredients, and use has to be sought in the literature.

Stability may be formulation-dependent and is likely to change with any manipulation of the product. Most studies base their expiry date recommendation on chemical stability but do not address possible physical or microbiological spoilage which may be significant during actual use of the product. Whereas compounded preparations will normally be freshly prepared, the storage and shelf life during use need to be considered, in particular if it becomes impractical to prepare the product immediately prior to dispensing each time it is needed.

The assignment of an expiry date serves to ensure suitability for use and will encourage regular fresh preparations. It also allows the practitioner to regularly review the patient's use of the preparation.

The following aspects should be considered when determining an expiry date:

- nature of the API and its degradation mechanisms;
- dosage form and its components;
- potential for microbial proliferation in the preparation;
- container in which the preparation is packaged;
- expected storage conditions; and
- the intended duration of therapy.

The in-use conditions, for example, access to a refrigerator for storage, should be taken into account when establishing the expiry date.

■ *Give clear instructions to caregivers and patients*

The instructions given to caregivers and patients may include instructions on storage, resuspension, changes in taste, smell, appearance, adverse effects and other pharmaceutical advice.

Compounded dosage forms are sometimes added to a small amount of liquid (e.g. water or juice) or sprinkled onto small amounts of food. Consideration should be given to the effect of food

on bioavailability and to the risk that only part of the dose will be swallowed. Provide parents and carers with appropriate information.

If an oral syringe or other measuring device is used it is important to check the technique to ensure that the correct dose is administered. Advise the use of clean measuring devices and explain how to avoid contaminating the preparation when preparing the dose.

- *Label information*

In addition to dosage instructions, include at least the following information, subject to national regulations for the labelling of medicines:

- if applicable, the name of the pharmaceutical preparation;
- the route of administration;
- the name(s) of the API(s) and excipients of known pharmacological action, and adverse effects, e.g. antimicrobial agents, antioxidants;
- if the preparation is a liquid, give the concentration(s) of the API(s), e.g. in mg/mL, and the amount or volume of the preparation in the container;
- if the preparation is a solid, give amount(s) of the API(s) in each dose and the number of doses in the container;
- reference or batch number (or date of preparation);
- expiry date (“do not use after ...”);
- any special storage conditions and handling precautions that may be necessary, e.g. “to be shaken before use”, “shelf life during use”;
- the pharmacy name and contact information;
- name of the patient.

Consider adding pictograms to supplement the label information, e.g. for “to be shaken well” and “store in the refrigerator”.

- *Document concerns and share information*

Practitioners are encouraged to maintain a dialogue with regulatory bodies and international agencies and networks about problems and concerns associated with the preparation and availability of age-appropriate medicines for children. The sharing of solutions to problems is also important.

## 5. Information, availability and access

A number of networks, websites and other resources are available which provide information on standards of practice, formulas for compounded preparations, manufacturers, suppliers of oral liquid formulations and responsive information services. These should be consulted by practitioners and regulators to enable them to provide the safest and most effective treatment options for children who require an age-appropriate formulation.

### 5.1 Standards of practice and guidelines

Some national, regional and international guidelines for extemporaneous formulations and medicines administration to children have been published. Consulting these documents may assist in forming local policies on practice and educational activities for practitioners.

### 5.2 Formularies and compendia

Formularies and compendia may be helpful in providing formulation advice and general advice on dosage manipulations. The information in these formularies may be difficult to transfer to a local situation where the base ingredients (e.g. commercial suspending bases, antimicrobial preservatives, pure API powder) are not readily available.

In addition to formularies and compendia, information can be sought in:

- the eMixt database ([www.pharminfotech.co.nz](http://www.pharminfotech.co.nz)), which provides comprehensive information for all settings and environments;
- *Handbook of extemporaneous preparations* (11), which contains formulations and associated stability summaries for oral liquid preparations;
- *Improving medicines for children*, by the Council of Canadian Academies, which contains a comprehensive review of paediatric medicines (14);
- The International Journal of Pharmaceutical Compounding, which is a general source of information. It is a subscription-only journal, but the contents can be searched on the journal's website (<http://www.ijpc.com>).

### 5.3 Source and supply

A database of sources and prices of medicines for children has been compiled by the United Nations Children's Fund (UNICEF) (15) and the UNICEF catalogue (<https://supply.unicef.org>) provides examples without being exhaustive.

Countries may also have their own database to use to find suppliers of age-appropriate formulations for paediatric use.

## 5.4 Networks and information services

- Local, national and international medicines information centres may respond to questions about formulation. One example is the WHO Paediatric medicines Regulatory Network (PmRN) ([http://www.who.int/childmedicines/paediatric\\_regulators/en/](http://www.who.int/childmedicines/paediatric_regulators/en/)). Partnerships and twinning arrangements between hospitals in poorly-resourced countries and developed countries can be explored and are often beneficial.
- Questions can be posted via the eMixt website ([www.pharminfotech.co.nz](http://www.pharminfotech.co.nz)).
- Sharing of information and advice on paediatric formulations should be explored whenever possible.
- International discussion lists can be useful for posting questions on formulations and their archives can be searched for previous questions and answers. Examples include eDrug and INDICES (accessed via [www.asksource.info/resources/essentialdrug.org](http://www.asksource.info/resources/essentialdrug.org)).

## References

1. Ernest TB, Craig J, Nunn A, Salunke S, Tuleu C, Breitzkreutz J, et al. Preparation of medicines for children – a hierarchy of classification. *Int Journal Pharm.* 2012;435(2): 124–30. doi: 10.1016/j.ijpharm.2012.05.070.
2. Nunn T, Hill S, Secretary, WHO Expert Committee on the Selection and Use of Essential Medicines. Report for WHO on findings of a review of existing guidance/advisory documents on how medicines should be administered to children, including general instructions on extemporaneous preparations and manipulation of adult dosage forms. Geneva: World Health Organization; 2011 (working document QAS/11.400 – available on request) ([http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/Review-findings-PaediatricMedicinesAdmin\\_QAS11-400Rev1\\_22082011.pdf](http://www.who.int/medicines/areas/quality_safety/quality_assurance/Review-findings-PaediatricMedicinesAdmin_QAS11-400Rev1_22082011.pdf), accessed 20 November 2015).
3. MODRIC. Manipulation of drugs for children – a guideline for health professionals. Liverpool: Alder Hey Children's NHS Trust ([http://www.alderhey.nhs.uk/wp-content/uploads/MODRIC\\_Guideline\\_FULL-DOCUMENT.pdf](http://www.alderhey.nhs.uk/wp-content/uploads/MODRIC_Guideline_FULL-DOCUMENT.pdf), accessed 20 November 2015).
4. Freeman MK, White W, Iranikhah M. Tablet splitting: a review of weight and content uniformity. *Consult Pharm.* 2012;27(5):341–52. doi: 10.4140/TCP.n.2012.341.
5. Development of paediatric medicines: points to consider in formulation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 5 (WHO Technical Report Series, No. 970).
6. Anon. Crushing tablets or opening capsules: many uncertainties, some established dangers. *Prescrire Int.* 2014; 23(152): 209–11, 213–14.

7. Smith S, Sharkey I, Campbell D. Guidelines for rectal administration of anticonvulsant medication in children. *Paediatr Perinatal Drug Ther.* 2001;4(4):140–7.
8. WHO good manufacturing practices: main principles for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986).
9. Good manufacturing practices for pharmaceutical products. In: Quality assurance of pharmaceuticals. WHO guidelines, related guidance and GXP training materials. Geneva: World Health Organization; 2015 CD-ROM.
10. Pharmaceutical Inspection Co-operation Scheme. PE 010-3 Guide to good practices for the preparation of medicinal products in healthcare establishments. PIC/S; 2014 (<http://www.picscheme.org/bo/commun/upload/document/pe-010-4-guide-to-good-practices-for-the-preparation-of-medicinal-products-in-healthcare-establishments-1.pdf>, accessed 20 November 2015).
11. Jackson M, Lowey A. Handbook of extemporaneous preparation: A guide to pharmaceutical compounding. London: Pharmaceutical Press; 2010.
12. Patel VP, Desai TR, Chavda BG, Katira RM. Extemporaneous dosage form for oral liquids. *Pharmacophore.* 2011;2(2):86–103.
13. Glass BD, Haywood A. Liquid dosage forms extemporaneously prepared from commercially available products – Considering new evidence on stability. *J Pharm Sci.* 2006;9(3):398–426.
14. Council of Canadian Academies. Improving medicines for children in Canada. Ottawa: The Expert Panel on Therapeutic Products for Infants, Children, and Youth; 2014 ([http://www.scienceadvice.ca/uploads/eng/assessments%20and%20publications%20and%20news%20releases/therapeutics/therapeutics\\_fullreporten.pdf](http://www.scienceadvice.ca/uploads/eng/assessments%20and%20publications%20and%20news%20releases/therapeutics/therapeutics_fullreporten.pdf), accessed 20 November 2015).
15. Sources and prices of selected medicines for children, including therapeutic food, dietary vitamin and mineral supplementation – 2nd edition. Geneva: UNICEF/WHO; 2010 ([http://www.who.int/medicines/publications/sources\\_prices/en/](http://www.who.int/medicines/publications/sources_prices/en/), accessed 20 November 2015).

## Further reading

The International Pharmacopoeia, fifth edition; 2015. Available online and CD-ROM version) (<http://www.int/medicines/publications/pharmacopoeia/en/index.html>).

Kastango ES, Trissel LA, Bradshaw BD. An ounce of prevention: Controlling hazards in extemporaneous compounding practices. *Int. J Pharm. Compounding.* 2003;7(5):401–16.

Pharmaceutical development for multisource (generic) pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 3 (WHO Technical Report Series, No. 970) ([http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/)).

Pharmaceutical Inspection Co-operation Scheme (<http://www.picscheme.org/>). In particular the following documents can be downloaded free of charge: PE 009-9 (Part I); PIC/S GMP guide (Part I: Basic requirements for medicinal products); PE 010-3 Guide to good practices for the preparation of medicinal products in healthcare establishments.

Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. Geneva: World Health Organization; 2008 ([http://www.who.int/selection\\_medicines/committees/expert/17/application/paediatric/Dosage\\_form\\_report\\_DEC2008.pdf](http://www.who.int/selection_medicines/committees/expert/17/application/paediatric/Dosage_form_report_DEC2008.pdf)).

The WHO Model formulary for children. Geneva: World Health Organization; 2010 ([http://www.who.int/selection\\_medicines/list/WMFc\\_2010.pdf](http://www.who.int/selection_medicines/list/WMFc_2010.pdf)).

# Appendix 1

## Examples of therapeutic alternatives to extemporaneous formulations

Required (available)	Possible alternative	Notes
diclofenac oral liquid (tablet)	naproxen oral suspension; ibuprofen oral liquid	The alternatives are available in some countries.
enalapril oral liquid (tablet)	captopril oral liquid (losartan oral suspension)	Captopril oral liquid is not available in all countries. Captopril has a shorter duration of action than enalapril. Enalapril tablets can be crushed and suspended in water immediately before use. Captopril tablets can be easily dispersed in water. Losartan may be appropriate for hypertension.
ibuprofen oral liquid (tablet)	paracetamol oral liquid	For pain and fever but not as an anti-inflammatory.
levamisole oral liquid (tablet)	albendazole chewable tablet; mebendazole oral liquid; pyrantel oral liquid	
lisinopril oral liquid (tablet)	ramipril oral liquid	
omeprazole oral liquid (capsule)	esomeprazole granules; lansoprazole orodispersible tablet	
praziquantel oral liquid (tablet)	niclosamide chewable tablet	Niclosamide can also be crushed and mixed with water to form a vanilla paste.
sertraline oral liquid (tablet)	fluoxetine oral liquid	

Table *continued*

<b>Required (available)</b>	<b>Possible alternative</b>	<b>Notes</b>
tinidazole oral liquid (tablet)	metronidazole oral liquid	Very few reasons why tinidazole should be preferred over metronidazole.
ciprofloxacin/dexamethasone ear drops	ciprofloxacin/hydrocortisone ear drops	

