1. Introduction and scope

Note
These guidelines are supported by a literature review of the evidence available (Annex 1). In this document reference is made to the relevant sections of the review for further information [provide web link here].

1.1 Background (to add)

In the context of neonatal and paediatric pharmacy practice, extemporaneous dispensing or preparation is the technique used by pharmacists to produce medicines from ingredients when no commercially available, authorised, age-appropriate dosage form exists. Compared to use of authorised medicines there are significant risks; quality, safety and efficacy can rarely all be assured and there have been many errors reported in the preparation of such medicines.

In some situations extemporaneous preparation of a medicine for a child may be the only option when there is no appropriate dosage form available but there may be other, safer and more effective ways of delivering the required dose and the risks associated with extemporaneous dispensing can be reduced when used as a last resort.

1.2 Purpose

The purpose of this guidance is to:

1. To provide evidence-based or best practice guidance and education about alternatives to extemporaneous preparation of medicines for children

2. To describe and educate practitioners in the potential problems of extemporaneous preparation and how to avoid them.

3. To provide brief best practice guidelines on extemporaneous preparation, if this is necessary as a last resort

4. To provide a bibliography of relevant literature, supporting evidence and existing guidance (by reference to the associated literature review).

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. Whilst the guidance is 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 guidelines will not reproduce areas where existing guidance and standards exist (e.g., GMP standards for facilities and documentation). Where appropriate, reference is made to the relevant resources and publications.

1.3 Target audience and healthcare settings

This guideline is intended for a wide audience of practitioners including

- All practitioners involved in the health care of children but mainly pharmacists, physicians, paediatricians and nursing staff.
- National drug regulatory authorities and professional bodies, e.g. national paediatric organisations, national pharmacy associations.
- General hospitals and health clinics
- Specialised paediatric hospitals and primary care clinics

It may be particularly useful in resource-poor situations where access to age-appropriate dosage forms is limited and where it may be difficult to obtain relevant information and/or achieve the highest standards of quality assurance when dispensing extemporaneous preparations.

2. Alternatives to extemporaneous preparation

The extemporaneous preparation of a liquid medicine from solid dose form (tablet or capsule) should generally be considered as a last resort and it is important to first consider alternatives that will give greater assurance of clinical effectiveness and safety. The risks and benefits of a particular dosing strategy should be evaluated on a case by case basis.

For example, if the stability and method of preparation of an extemporaneous oral liquid are well documented and all the facilities and ingredients are available it may be less compelling to seek an alternative. On the other hand, if there are no stability data and the drug forms a caking suspension in the only available excipient (syrup), an alternative must be considered to ensure safe and effective treatment.

The main alternatives to consider are:

a. **Sourcing of a commercially available or *manufactured product if available.**

The logistics of supply and access are obvious factors that might mitigate against this but practitioners should liaise with suppliers, importers and regulatory authorities to access these products if possible. If there is going to be a continued requirement for the product local registration can be sought through the appropriate channels.

Importation of products may be expensive and reputable suppliers should be used to avoid counterfeits. Quality assurance systems should be in place, for example, to ensure that recall systems are available and information provided in the local language.

The large scale use of a extemporaneously prepared oral liquids for children should not be justified on the grounds that they are cheaper than commercial products. Other options, including local manufacture using GMP standards, should be investigated.

* This includes products prepared to GMP standards, for example in an accredited hospital manufacturing unit or specials laboratory.

b. ‘dose rounding’

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

Some drug 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 weight or age band. Consult the WHO Model Formulary for Children [provide web address].

c. **Therapeutic alternative**

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

d. **Pharmaceutical alternative**

Consider strategies to increase assurance that a more effective and safer product can be delivered. There are a number of alternatives to extemporaneously preparing an oral liquid especially if the stability of an oral liquid cannot be assured. These include;
(i) Tablet splitting
Tablets can be split, either by breaking if scored or by using a purposely designed tablet cutter. If the child is able to take solid dose forms safely (usually from age 8 and above), the tablet fraction can be given, otherwise it can be dispersed or mixed with food or juice as below.

Not all tablets split uniformly and the content of the active ingredient may not be distributed uniformly throughout the tablet. Thus, consider on a case by case basis whether splitting tablets might lead to toxicity or reduced effect [refer to relevant section in literature review].

(ii) Tablet dispersion
It may be possible to disperse tablets in water or other liquid. If the tablet disperses, it can be dispersed in a small volume and the whole dose given when a suspension is formed, mixed with a flavoured vehicle if required. Not all tablets disperse readily but some form a suspension in seconds.

If the tablet disperses readily and the drug is known to be soluble, dispersing the tablet in a known volume of water can allow a fractional dose to be accurately measured with a syringe as in the case of captopril. As extraction of soluble drug from the tablet excipients may be incomplete the suspension should be shaken or stirred prior to measuring the dose and not filtered unless it has been established that active drug is not removed. In the case of an insoluble drug, the measurement of a fractional dose by taking an aliquot from a suspension formed in this way cannot be recommended due to probable rapid sedimentation of insoluble drug and resultant dosage inaccuracy. Tablet dispersion may not always be practical for infants when the doses required are the equivalent of small tablet fractions that are unable to be reliably prepared, e.g. a fifth of a tablet, or if the tablet is not scored.

WHO is promoting the use of flexible solid oral dosage forms such as dispersible tablets. The use of custom made dispersible tablets for paediatric dosing should be used wherever possible but there is a need to ensure that carers understand how they are to be administered.

(iii) Crushing tablets/opening capsules and mixing powder with food or a drink
The practice of crushing tablets or opening capsules and adding the powder to a palatable drink or sprinkling onto solid food is a time-honoured alternative, but there may be little evidence to support efficacy (since stability and bioavailability may be altered). If this is to be done then information should be sought from manufacturers (e.g. oseltamivir) and formularies whenever possible. It is also difficult to ensure that a complete dose has been taken and the practice of nurses or carers handling powdered drug may present health concerns. Tablet dispersion may be a simpler, more reliable and potentially safer method.

(iv) Giving the injectable form by the oral route
This is possible for some drugs but there are important factors which must be considered when evaluating whether the injection is suitable for oral use. It is recommended that specialist advice, e.g. consultation with a medicines information center is sought before this alternative is considered. Some examples are described in Appendix 2

3. Extemporaneous preparation

3.1 Potential problems and how to avoid them

Extemporaneous formulation is associated with a number of potential problems that may impact on the safety and effectiveness of the preparations. An awareness of the relative complexity of formulation and the things that can go wrong will help to avoid such problems. A more detailed overview of the issues is given in Appendix 4
3.2 Basic considerations for extemporaneous formulation

- Consider extemporaneous formulation as a last resort
  Always explore alternative strategies for preparing and giving the dose especially if the preparation of an effective and safe preparation cannot be assured.

- Consider using an authorised dosage form as the starting point
  It may be safer and more effective to crush tablets or use the contents of capsules with and appropriate suspending vehicle rather than preparing from active ingredient chemicals and excipients. There are many formulations available with validated shelf life but sourcing of suspending agents may be difficult and/or expensive.

- Consult literature and guidelines if available
  If possible, always use a validated formulation (i.e. based on literature, stability studies and guidelines). Consult the latest national and international guidelines and/or specialist information centres if possible.

- Employ the principles of Good Manufacturing Practice
  This involves the processes put in place to give the highest level of assurance possible that the product will be effective and safe when administered to the patient. It is accepted that few units will be able to conform to the requirements of a GMP facility. However, the principles of quality assurance are possible and essential under any conditions. Further guidance is given in Appendix 3.

- Dose uniformity may be a problem - explain importance of re-suspension
  If the drug is insoluble, it will generally be more chemically stable in a liquid formulation but uniformity of dosing may be a problem. A suspending agent will be required. Always check that the finished preparation re-suspends under in-use conditions and explain the importance of re-suspension to patients/carers.

- Shake all preparations before the dose is given
  If the drug is soluble it will generally be less stable in a liquid preparation. As the drug is soluble the inclusion of a suspending agent is less important. As excipients and other formulation components can affect solubility ALL extemporaneous formulations should be shaken prior to administration as all drug may not be in solution even if it is highly soluble. The only exception would be if the preparation is made from pure drug and it can be assured that all the drug is in solution.

- Caution in extrapolating from other formulations
  Caution is required if extrapolating the formulation from a published study or formulary. Formulations made from pure drug 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 drug in an oral liquid preparation. The salt form of the drug used in a published study could be different to the form locally available and this may affect the drug’s solubility and stability. Consult specialist advice if possible. Similarly, the results of a published study using a drug mixed with a commercial suspending base (e.g. Ora-Plus) cannot generally be extrapolated to a situation where the same drug is mixed with a simple base of syrup or glycerol.
• **Exceptionally, when no published formulation is available**
  The pharmacist must assess the risks for different options and use knowledge and experience to formulate a product
  
  o **Obtain physicochemical properties of the drug if available**
    Drug solubility and pH stability profile may be useful when considering the approach to formulation or dose administration. If possible, obtain basic physicochemical information about the drug, especially the aqueous solubility of the drug at the expected concentration in the final product.
  
  o **Test the physical characteristics prior to patient use**
    Tablet/capsule formulations vary worldwide (especially with respect to excipients content) and ingredients used in formulations also vary. These differences can influence the effectiveness and acceptability of the preparation. Basic performance tests should be performed before patient use, particularly on formulations prepared for the first time. This includes; ease of re-suspension and pouring, degree of caking on storage, observation of physical behaviour and characteristics
  
  o **Consider risk of microbial growth**
    All extemporaneous formulations are highly susceptible to microbial growth. An antimicrobial preservative must be included unless the final product will be used completely within 2-3 days and stored under refrigeration. Oral liquids that are not adequately preserved will support rapidly growth of bacteria and fungi especially at warm to hot temperatures and can pose hazards to patients especially if immunospressed.
    Preparation of extemporaneous liquids should be carried out under conditions to minimise the introduction of microbial contamination  *(See Appendix 3)*

• **Use appropriate final containers**
  Final containers and closures should be clean and free from dust and other residues.
  Containers that have been re-used 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.

• **Consider in-use storage**
  The in-use storage conditions may vary considerably from those in a published study or formulary recommendation. Always consider if it will be possible to store and use the preparation under the optimal conditions described in the study, which usually are refrigeration, protection from light and with 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 (e.g. from one month to one week) according to professional judgement. If possible consult expert advice.

• **Expiry dates and shelf-life**
  The chemical stability and potential for microbial growth under real patient use are seldom tested in published studies. It is recommended that an expiry date of a maximum of one month (or less if advised in the published study or if antimicrobial preservatives cannot be used) is applied to all extemporaneous formulations. This will encourage regular fresh preparation and help to assure effectiveness and safety. It also allows the practitioner to regularly review the patient’s use of the preparation.
• **Give clear instruction to caregivers/patients**
  This may include instructions on storage, re-suspension, changes in taste, smell or appearance and adverse effects. If an oral syringe or other measuring device is used it is important to check technique to ensure the correct dose is administered. Advise the use of clean measuring devices and ways to avoid contaminating the preparation when preparing the dose.

• **Document concerns and share information**
  Practitioners are encouraged to maintain dialog 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.

### 4. Information, availability and access

A number of networks, web sites and other resources are available which provide information on standards of practice, formulas for extemporaneous preparation, suppliers of oral liquid formulations and networks and responsive information services. These should be consulted by practitioners and regulators to provide the safest and most effective treatment options for children who require an age – appropriate formulation.

#### 4.1 Standards of practice and guidelines

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

[Also list here, GMP guidance, Jackson and Lowery](#)?

#### 4.2 Formularies and compendia

These 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 drug powder) are not readily available.

The eMixt database ([www.pharminfotech.co.nz](http://www.pharminfotech.co.nz)) is being developed to provide comprehensive information for all settings and environments. *(Other resources include; (Can we drag from the review, or list a few good ones?))*

#### 4.3 Source and supply

A database of sources and prices of medicines for children has been compiled by UNICEF. This will be available electronically by mid-2011.

[http://www.unicef.org/supply/index_47129.html](http://www.unicef.org/supply/index_47129.html)

The data base can be searched to find worldwide suppliers of oral liquids and other age appropriate formulations for paediatric use.
4.4 Networks and information services

4.1 Local, national and international medicines information centres may respond to questions about formulation. Partnerships and twining arrangements between hospitals in poorly resourced countries and developed countries can be explored and are often beneficial. Question can also be posted via the eMIxt web site www.pharminfotech.co.nz

4.2 Sharing of information and advice on paediatric formulations should be explored whenever possible.

4.3 International discussion lists can be useful for posting questions on formulations and the archives can be searched for previous questions and answers. Examples include; eDrug and INDICES accessed via; http://www.essentialdrugs.org/

4.4 It is recommended that an international repository of questions and answers on issues relating to medicines administration for children be set up which will promote the sharing of information, problem solving, best practice and educational awareness. This will also help to identify research projects that can be directed toward academia and industry.

5. Guidance for regulators and suppliers

5.1 Regulators should work with practitioners (pharmacists, physicians, paediatricians) to source age-appropriate formulations.

5.2 If possible, therapeutic and pharmaceutical alternatives (including dispersible tablets) to extemporaneous formulation should be sourced.

5.3 International networks and resources such as the UNICEF Virtual Warehouse and the eDrug discussion list should be consulted for advice on suppliers and access the age appropriate formulations.

6. Guidance for researchers

Ongoing research on extemporaneous formulation is important. However most studies published to date have been carried out using commercial suspending bases that are not widely available. It is not usually possible for practitioners to extrapolate the results of these studies to formulations using simpler ingredients that may be the only alternative to a commercial base. Researchers are encouraged to perform parallel studies using simple ingredients that may be more widely available.

7. Further information

Some practice scenarios are outlines in Appendix to explain some of the principles described above.
# Appendix 1

## Examples of therapeutic alternatives to extemporaneous formulation

<table>
<thead>
<tr>
<th>Required</th>
<th>Possible alternative</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril liquid</td>
<td>Captopril liquid</td>
<td>Available commercially in some countries.</td>
</tr>
<tr>
<td></td>
<td>Dispersed captopril tablets</td>
<td>Captopril tablets can be easily dispersed prior to giving the dose</td>
</tr>
<tr>
<td>Naproxen oral liquid</td>
<td>Ibuprofen liquid if available</td>
<td>NSAID may not be clinically justified.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paracetamol may be a suitable and safer alternative</td>
</tr>
<tr>
<td>Felodipine oral liquid</td>
<td>Dispersed amlodipine tablets</td>
<td>Amlodipine is very soluble and fractional doses can be prepared.</td>
</tr>
<tr>
<td>Tinidazole oral liquid</td>
<td>Metronidazole oral liquid</td>
<td>Very few reasons why tinidazole should be preferred over metronidazole</td>
</tr>
</tbody>
</table>

**ANY MORE EXAMPLES?**

In some cases the therapeutic alternative may not be available as an oral liquid but as a more easily manipulated form (see felodipine example above).

Oseltamivir oral suspension v capsule contents in water

PPI example?
Appendix 2

Oral administration of injections – examples and considerations

If the injectable form of the drug is the same as the oral form (for example labetalol hydrochloride, ondansetron hydrochloride) it can be assumed that the drug will be absorbed from the injectable formulation. However, as the drug is in solution more rapid absorption and higher peak levels may occur compared to slower absorption from a solid dose form.

Some injectable drug forms are produced by reaction of the insoluble oral form with sodium hydroxide to give a soluble salt (for example acetazolamide sodium, sodium folate). In the acidic conditions of the stomach the oral form (acetazolamide, folic acid) will be generated.

The injectable form of drugs which are chemically degraded by gastric acid (for example omeprazole) are unsuitable for oral administration.

The oral use of the injectable form of a drug which is subjected to extensive first-pass metabolism, resulting in poor oral bioavailability, may be impractical due to the large volume required. For example, a volume of 15 mL (15 ampoules) of 1 mg per mL is required if propranolol injection is used to give an oral dose of 15 mg.

Drugs such as cefuroxime and enalaprilat which are administered orally as pro-drugs (cefuroxime axetil and enalapril maleate) have relatively poor bioavailability and are not suitable for oral administration.

Injections may contain excipients and adjuvants that are undesirable in some patients. For example, propylene glycol and ethanol.

The cost of using the injectable form orally may be prohibitive. For example, the cost of giving dantrolene injection orally is approximately 60 times the cost (per mg of drug) of using the oral form.
Appendix 3  *(need to add this but very basic)*

Guide to GMP for extemporaneous formulations
Appendix 4

Extemporaneous formulation – Consideration of the potential problems.

If an alternative to extemporaneous formulation is not possible it is important to be aware of the potential problems involved in this practice and how to avoid these pitfalls.

The most frequently used method is to grind the required number of tablets to a fine powder in a mortar and form a slurry by adding a small volume of water. At this stage there is the potential for the operator to be exposed to hazardous powdered drug and microbial contamination of the product if clean equipment is not used.

Excipients such as antimicrobial preservatives, suspending agents and flavouring agents are added to make the final product. A frequently used base is a mixture of glycerol or syrup, a suspending agent such as methylcellulose, and para-hydroxybenzoates (parabens) as a preservative. Other agents sometimes added include alternative solvents such as ethanol, particularly when the drug is poorly soluble in water, and buffer systems to provide the optimum pH for drug stability or activity of the antimicrobial preservative. Whilst ostensibly simple, such formulations can be complex comprising a mixture of the base and a suspension or solution (usually a combination of both) of tablet excipients and active drug. If the drug is water soluble there is a temptation to filter out the insoluble tablet excipients to leave a clear solution but filtration can remove significant amounts of drug if extraction from tablets is incomplete. Insoluble tablet excipients are in suspension and may compromise product appearance whereas soluble excipients may alter drug stability, for example, by changing the pH of the preparation. Whilst there may be advantages in using pure drug powder instead of tablets it may not be easily obtainable.

The expiry date or "shelf-life" of an extemporaneously prepared oral liquid is assigned empirically or based on published information on a particular formulation. A conservative approach must be adopted when assigning an expiry date because of lack of information on drug stability or limitations in either the design or the conclusions of a published report. Also, it may be impractical to entirely reproduce the conditions of a study which was performed in another institution or country under the controlled conditions of an experiment rather than clinical use. 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. For these reasons it is the author's opinion that extemporaneously prepared oral liquids should only be used for a maximum of one month from the date of preparation to minimise any unrecognised product deterioration. Longer expiry dates may be applied if more extensive testing is performed.

Finally, when deciding on a formulation it is important to consider any possible adverse effects of the "inactive" components of the preparation. Sucrose (in syrup) can promote the formation of dental caries, ethanol can cause hypoglycaemia and para-hydroxybenzoates can cause hypersensitivity reactions and exacerbate the symptoms of asthma. It has also been suggested that benzoates and para-hydroxybenzoates can aggravate neonatal hyperbilirubinaemia by displacing bilirubin which is bound to plasma proteins but this effect has not been demonstrated in vivo and the amounts present in oral formulations are unlikely to pose any risk. Limits for the inclusion of ethanol in paediatric formulations have been proposed by the American Academy of Pediatrics.
Deterioration of an oral liquid may be due to chemical, physical or microbiological instability which can lead to a sub-therapeutic dose of drug, exposure to toxic degradation products or ingestion of unacceptable numbers of micro-organisms. It is important for pharmacists, clinicians and nursing staff to be aware of potential problems caused by instability to ensure that drug therapy is effective and safe.

**Chemical instability**

Drugs in extemporaneously prepared liquids may be susceptible to chemical reactions leading to degradation. The most common reactions are hydrolysis, oxidation and reduction.13 Usually the reaction rate or type is influenced by pH, for example, azathioprine is rapidly hydrolysed to 6-mercaptopurine at alkaline pH but is relatively stable in acidic or neutral conditions.22 Other factors which may increase the rate of reaction include the presence of trace metals which catalyse the oxidation of captopril11 methyl dopa12 or exposure to light which catalyses the oxidative degradation of 6-mercaptopurine.22 The rate of chemical degradation usually increases with temperature, a factor which is the basis for accelerated stability trials of pharmaceutical formulations. Preparations made from tablets contain excipients such as binders and disintegrating agents in addition to the active drug. 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 drug is more stable than an oral liquid prepared from tablets.16

The drug in the preparation may be totally or partially in solution or predominantly in the solid state as a suspension. Drugs in solution are more susceptible to chemical degradation than drugs in the solid state (ie. suspensions), thus suspensions of acetazolamide and chlorothiazide are more stable than solutions.35,36 However it cannot be assumed in all cases that an extemporaneously prepared suspension is more stable than a solution. In a suspension, an equilibrium exists between drug in the solid state and drug in solution and even though the amount of drug dissolved may be minimal the conditions could be optimal for degradation. Frusemide is a notable example which 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.16

**Microbiological Instability**

Microbial growth in an oral liquid may cause foul odour and turbidity and adversely effect palatability and appearance. High titres of micro-organisms 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 drug. Microbial contamination during preparation must be minimised by using clean equipment, sterile water (Water for Irrigation BP) and 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 unionised form is predominant.22 Consequently the drug must also be stable at this pH.

Effective preservative systems require rigorous evaluation which is seldom performed on extemporaneous formulations. 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.

**Physical Instability**

Extemporaneously prepared oral suspensions may be susceptible to sedimentation of insoluble drug causing caking. Difficulty in re-suspending the drug or rapid sedimentation following shaking can lead to erratic dosage measurement as demonstrated with chlorothiazide suspension28 and this inherent problem with extemporaneously prepared formulations is of
considerable concern. Some spironolactone suspensions have been reported to be excessively thick and almost un-pourable. Refrigeration, whilst usually desirable to maximise chemical stability and reduce microbial growth, can also increase the viscosity of a suspension making re-suspension more difficult or cause the precipitation of active drug or preservatives. It is important to consider the effect on pH of all components of the formulation and the possible impact on stability. Syrup, for example, is relatively acidic and if used in phenobarbitone sodium oral solution it will cause the precipitation of unionised phenobarbitone.
Appendix 5  Practical examples

Vigabatrin

A dose of 20 mg/kg twice daily for a 10 kg child requested, ie. 200 mg twice daily.

Background.
No therapeutic alternative considered desirable. Vigabatrin preferred.
No oral liquid available and no information on extemporaneous formulation. BNF and other reference texts mention powder sachets are available for reconstitution prior to giving the dose, but these are not available in your country.

Action; If on-going need is anticipated investigate source and supply of Vigabatrin Sachets

Information in Martindale, other standard texts or internet search state that vigabatrin is feely soluble in water. You also do a simple test and ascertain that the brand of vigabatrin tablet that you have available disperses rapidly in water.

Action;
Advise on dose preparation as follows; disperse 500 mg tablet in 10 mL of water and stir to ensure that the drug is dissolved, leaving only insoluble excipients.
Measure out 4 ml to correspond to 200 mg vigabatrin and give to patient mixed in a flavoured juice if necessary. Discard any remaining liquid as stability of vigabatrin on storage is unknown.
NB even though all the drug should be in solution, agitate the liquid before giving the dose as soluble drug may be bound to insoluble excipients that may be in suspension.

After one week, the dose is increased to 25 mg/kg twice daily. The dose is now 250 mg twice daily, which equivalent to half a tablet. The 500 mg tablets are scored.

Action;
Instruct the carer to break the tablets in half (this could be done by the pharmacy in advance). Disperse half a tablet (250 mg) in water and give the dose immediately. Save the remaining half tablet for the next dose.
Outline of report for WHO on findings of document review

Task

1. To review existing guidance/advisory documents on how medicines should be administered to children, including general instructions on extemporaneous preparations and manipulation of adult dosage forms.

2. Prepare a report of the findings of the document review for WHO

3. Using the findings of the review prepare a short summary document detailing the scope for the planned guidance document on how medicines should be administered to children

4. Prepare a draft guidance document that can be assessed by the Expert Committee on Selection and use of essential medicines, to improve use of medicines in children.

1. Introduction

1.1 Many of the medicines required for children are not available in authorised, age-appropriate formulations (1,2). A recent survey of EU Member States conducted by the European Medicines Agency concludes that the prescription of off-label and unlicensed medicinal products is still widespread in Europe, both for inpatients and outpatients, with higher rates in very young children and children with very severe conditions (3). One important reason for off-label and unlicensed use in children is the lack of age-appropriate formulations: Those medicines that are appropriate may not be available in the countries that require them (4).

1.2 This problem of poor access may be overcome in several ways including importation of age-appropriate formulations; extemporaneous preparation (or compounding) from other authorised dosage forms or from active drugs and excipients; and manipulation of other dosage forms in an attempt to provide an accurate paediatric dose (12).

1.3 When the therapeutic index of a drug is large, prescribers, dispensers and administrators may also adopt strategies such as ‘rounding’ the dose to that of a convenient dosage form (e.g. oral amoxicillin, oral omeprazole when a large dose range of 0.7-3mg/kg/day often means the dose can be rounded to enable a MUPS tablet to be used) or therapeutic substitution of a similar drug for which a more appropriate dosage form is available (example or reference required). Evidence for these practices is mainly confined to adults (MI reference).

1.4 The alternatives to using an authorised, age-appropriate dosage form are all associated with different degrees of risk to the patient. Extemporaneous preparation, with little if any quality assurance, carries significant risk of error, unknown efficacy and toxicity and there are many reports of significant harm (5, 6).

1.5 Extemporaneous preparation or dispensing is poorly defined and may also be known as ‘compounding’. A working definition used by Brion et al (7) is ‘the manipulation by pharmacists of various drug and chemical ingredients using traditional compounding techniques to produce suitable medicines when no commercial form is available’. The terms ‘compounding’, ‘magistral’ and ‘officinale’ preparation may also be used (see glossary).
1.6 This paper reviews the literature providing standards and guidelines for extemporaneous preparation\(^1\) and manipulation of dosage forms to provide accurate paediatric doses and considers guidance on strategies to avoid extemporaneous preparation. Where secondary guidelines are not available some of the primary literature has been reviewed. The paper will inform guidelines and recommendations to the WHO expert committee on the Essential Medicines List.

2. Access to age-appropriate formulations

2.1 Some paediatric age-appropriate medicines (e.g. oral liquids) are authorised and available in countries which have high standards of regulatory control giving assurance that the medicine is of appropriate quality and that safety and efficacy have been assessed as appropriate (e.g. carbamazepine liquid, folic acid syrup)

2.2 Information for healthcare professionals will be provided in the summary of product characteristics (SmPC; EU) or label (USA) or similar document approved by the regulator. Information for carers may also be provided using patient information leaflets from the manufacturers. Patient information for unlicensed and off-label medicines may be specially prepared by pharmacists and doctors (for examples on the Medicines for Children website www.medicinesforchildren.org.uk).

2.3 However, manufacturers may not make their medicines available in all countries even within a defined region (7).

2.4 Obtaining information on the availability of suitable paediatric medicines is difficult and there may be economic and other reasons why they cannot simply be imported into countries requiring them.

2.5 UNICEF global virtual warehouse

UNICEF publishes information on the availability and cost of many medicines (9). It can be difficult to make such information comprehensive and up-to-date so UNICEF, companies and wholesalers should be contacted to ascertain the current situation.

2.6 Specialist importers/exporters of medicines

In some countries the import and export of medicines requires regulatory licensing. Specialist companies will be able to source medicines and make arrangements for their transport. Sourcing of medicines may be free-of-charge if an order seems likely but the overall cost of the service provided may be expensive.

2.6.1 In the UK, the medicines regulator (MHRA) has recently changed the way in which appropriately authorised wholesaler dealers and manufacturers can make healthcare professionals aware of the imported and other unlicensed medicines they have available (10). This includes the availability of medicines licensed in other countries and may make dissemination of such information easier.

CPA survey of Anglophone African countries

\(^1\) This paper does not set out to consider manufacturing of medicines to Good Manufacturing Practice standards accepted by WHO or national medicines regulatory agencies. Sometimes the distinction between extemporaneous preparation/compounding, small scale manufacture and manufacture to GMP standard may be blurred.
4. Options when age-appropriate formulation not available

4.1 Therapeutic substitution (12, 15, 26)

In the absence of an appropriate formulation for a particular medicine, it may be appropriate to consider the use of an alternative drug of the same class. Certainly, the use of a licensed medicine from the same therapeutic classification may provide a better clinical option than the use of an extemporaneously prepared medicine that has limited data to support its formulation and stability.

However, in practice in the paediatric population, the possibilities are very limited. Where alternative agents are suggested, therapeutic equivalence cannot be assumed. Patients will require monitoring and possibly dose titration when switching e.g. in adults who cannot swallow sertraline tablets, switching to licensed fluoxetine liquid may be viewed as a better and safer option than crushing sertraline tablets.

4.2 Rounding of doses

4.2.1 The doses for many paediatric medicines are quoted in dosage guides or formularies in mg/kg body weight. Having multiplied by body weight, the dose calculated may not correspond to a dosage form which is available (e.g. tablet, capsule). For medicines with a wide therapeutic index it may be possible to round the dose to the dosage form available without compromising safety or efficacy (e.g. some oral antibiotics, oral omeprazole, and mefloquine).

4.2.2 Several treatment guidelines and formularies recognise this and publish dosing advice which allocates an appropriate dosage form and strength to a band of weights. Examples include oral amoxycillin tablets for pneumonia and anti-retrovirals for the treatment of HIV in infants and children (11) [reference].

4.2.3 If formulary guidance is not available the pharmacist should use experience and knowledge of the characteristics of the drug to know whether it is safe to round doses.

4.2.4 However, the necessary pharmacokinetic and or pharmacodynamic evidence to support this practice may not be available.

4.3 Using an authorised medicine in an ‘off-label’ manner

4.3.1 Authorised medicines used in ways other than those covered by the SmPC or label are said to be used ‘off-label’ (e.g rectal paraldehyde, sublingual lorazepam, buccal midazolam using the injection solution).

4.3.2 Medicines are frequently used ‘off-label’ for children, perhaps for a different age range, a different indication, administered by a different route or the dosage form is manipulated to provide an accurate dose for a child.

4.3.3 When medicines are used ‘off-label’ there should be adequate information available to support the practice (e.g. some ACE inhibitors such as enalapril and lisinopril are not licensed for use in children (or restricted to certain ages) but there is dosage information in publications such as the BNFc to support use).

4.3.4 Medicines administered by different routes or manipulated to provide an accurate dose run the risk of errors in preparation, dispensing or administration. The bioavailability of such manipulations is unpredictable and there may be no compatibility or stability data available.

4.3.4 Young children are often not capable of alerting health care professionals or carers to any adverse drug effects they may be experiencing.
4.3.5 Manufacturers may not be prepared to provide relevant information when medicines are not used according to their authorisation but their information departments should be consulted.

[something more on sources of information?] In addition, establishment of good links between paediatric centres both nationally and internationally allows dissemination of clinical experience and practice that can be of real value.

4.4 General guidelines on alternative routes of administration

(i) Use of a preparation intended for a different route

It may be possible to use a licensed formulation via an alternative route e.g. use of an injection solution by the oral route or the use of oral liquids rectally but there are important factors that must be considered

- Use of an injection solution orally
  The following factors should be considered (12, 13, 14, 15)
  - will the IV form be absorbed via the enteral route? If the injectable form of the drug is the same as the oral form e.g. ondansetron hydrochloride, it can generally be assumed that the drug will be absorbed from the injectable form (12). However, differences in the pharmacokinetics should be anticipated as more rapid absorption is likely from a solution.
  - oral use of an injectable solution that is chemically degraded by gastric acid is not an option as they will have very poor oral bioavailability
  - will the pH of the solution be tolerated? Extremes of pH could adversely affect the gastric mucosa
  - does the injectable form contain any excipients that may be harmful? Some injection solutions contain propylene glycol and ethanol which can be problematic if large volumes are required
  - taste may be an issue
  - Large volumes may be needed to achieve the recommended oral dose
  - Cost may be prohibitive

- Oral liquids administered rectally (16)

For children unable to take medicines by the oral route, it may be possible to administer oral liquids by the rectal route. There are not a great number of medicines available in suppository form and suppositories offer largely inflexible dosing. It is suggested that the use of liquids rectally allows improvement in the flexibility of dosing and allows maximal rectal and colonic mucosal contact resulting in rapid and complete absorption. Rectal absorption occurs by passive diffusion across a lipid membrane as in the rest of the GI tract. The extent and rate of absorption are optimal if the drug is lipid-soluble and non-ionised. In their guidance on rectal administration of anticonvulsants, Smith et al suggest consideration of the following factors in assessing the suitability of a drug for rectal administration:

- Absorption from the GI tract: drug which exhibits good absorption via the oral route can be expected to be well absorbed from the rectum (passive diffusion)
- Degree of first pass metabolism: given rectally a proportion of drug in the lower part of the rectum avoids first pass metabolism. If a drug given orally exhibits significant first pass metabolism high doses are often needed to compensate – if given rectally at the same dose as oral this may result in toxicity and consideration should be given to reducing the rectal dose. If however first pass metabolism is not significant, the rectal dose can be assumed to be approximately equivalent to the oral dose.
- Osmolarity: consider dilution of the solution/suspension if of high osmolarity to minimise the urge to defecate
It is also possible to administer some IV formulations by the rectal route e.g. rectal paraldehyde in status epilepticus. The presence of propylene glycol in some parenteral solutions may increase rectal absorption due to its lipid solubility.

Conclusion

There is only limited information available but rectal administration of oral liquids or suspensions (including crushed tablets in water) may be an option in those children unable to take medicines orally. Consideration should be given to the rectal volume (this varies with age and will affect the volume that can be instilled) and the rectal length (to determine the distance at which the enema catheter should be inserted). The rectum should be evacuated before drug administration. Administration of the enema into the distal rectum should permit predictable absorption whilst minimising the risk of perforation.

4.5 General guidelines on manipulating dosage forms for accurate administration of doses to children

In the UK, an expert panel has started to develop a guideline on the manipulation of medicines to deliver accurate and reproducible doses to paediatric patients where no suitable age appropriate product is available.

4.6 Guidance on specific manipulations

4.6.1 Segmenting tablets

Segmentation of tablets into halves and quarters is a relatively common practice in the pharmacy, on hospital wards or at home to try and obtain a segment containing an appropriate child dose from an adult solid dose formulation. There are anecdotal reports of tablets being split into as many as 8 or 10 pieces in an attempt to provide an accurate paediatric dose from ‘adult’ tablets.

To ensure an accurate dose, the practice of segmenting tablets assumes there is uniform distribution of the active drug within the tablet and also the ability to segment the tablet accurately.

Segmenting tablets may be an option especially with those tablets that are scored and it is suggested that these segments probably have similar stability to the original tablet (14). Such a practice is relatively straightforward and does not have any significant cost implications.

However, some studies suggest that tablets cannot actually be cut with great efficacy (even with the use of a tablet cutter which would not be readily available in some countries). This could have a significant effect on the patient, particularly for those drugs with a narrow therapeutic index when an insufficient dose could lead to treatment failure and a larger than expected dose lead to toxicity.

Teng J (17) looked at the division of 11 commonly split tablets and evaluated the resulting half-tablets for content uniformity using the USP Uniformity of Dosage Units test (18). Of the 11 tablets, which were split with a razor, 8 failed this test. It was noted that no visible tablet features (e.g. scoring) predisposed a product’s split segments to pass or fail the uniformity test. All 3 hand-split tablets failed the uniformity test and yielded worse results than did razor-split tablets.

Shah et al (19) considered the tablet splitting of levothyroxine, a drug with a narrow therapeutic index and confirmed the results found by Teng in that split tablets either by hand or by the use of a tablet cutter showed a higher rate of content uniformity failures as compared to whole tablets. They also noted that use of a tablet cutter produced more fragmentation and hence, more content
uniformity and friability failures. They did however note that splitting of tablets did not have any measurable impact on the stability.

Rosenberg et al (20) determined the level of weight uniformity of segments from tablets cut into halves and dispensed by pharmacists. 560 split tablet halves were collected and their weights, determined and using criteria from the USP for weight variation of whole tablets, identified that tablet splitting resulted in an unacceptably high incidence of weight variation.

In their recent study, Verrue et al (21) reported on dose deviations and weight losses while splitting tablets in the nursing home setting. Five volunteers split 8 tablets of different sizes and shapes using (i) splitting device (Pilomat\textsuperscript{3}), (ii) scissors for unscored tablets or manual splitting for scored tablets and (iii) a kitchen knife. For all tablets, the use of a splitting device gave a statistically lower mean deviation from theoretical weight.

Segmenting modified release or sustained release tablet formulations is not usually considered an option as destruction of this matrix could significantly alter the pharmacokinetics of the formulation. However, there are some slow release formulations e.g. Pentasa (mesalazine) for which there is information to advise that tablets can be halved and quartered without any adverse effect on the matrix system. These segments must not however be chewed.

It is worth contacting individual drug manufacturers for advice on individual products, although some are more willing than others to provide such information if it is outside the product licence.

Conclusion (to go forward as a recommendation)

Splitting tablets may lead to considerable inaccuracy in dose delivery and the ability to undertake this successfully may relate to the pharmaceutical properties of individual products, the ability of the operator and the device used for cutting. Manufacturers could assist by providing appropriate tablet geometry, uniformity of content and validating splitting into segments of a size known to be used for children. WHO/UNICEF should consider which tablets are most frequently manipulated in this way and seek assurances from manufacturers.

In the meantime, advice is:

If only ‘adult’ tablets are available the pharmacist or clinician should check to see if they can be split (in general, sustained release or enteric coated tablets should not be split). If possible tablets with appropriate score lines should be sourced and used and the manufacturer should be contacted to confirm content uniformity when segments are produced and to establish if there is information on stability of segments. Segments should be cut using a commercial tablet splitter (e.g. Pilomat\textsuperscript{3}) by the health care worker if possible and segments carefully packaged to protect their integrity. When this is not possible carers should be instructed on the method of preparing and storing tablet segments. Due regard should be given to the therapeutic index of the drug when considering splitting of tablets.

4.6.2 Opening capsules / crushing tablets

Even if an appropriate dose can be achieved from segmenting tablets, solid dose formulations are often still not a practical option for administration to children. It is suggested that only from around 6 years of age will children be able / willing to try swallowing a solid dose and so consideration must be given to crushing the tablet (or segment) or opening a capsule to take the powder or liquid content. (12, 22)
It is important to remember that the act of crushing tablets or opening capsules which are not designed to be administered in this way, alters the formulation of the medication and may, potentially, have a negative effect. The rate or site of absorption and bioavailability of the active drug may be affected. This is very significant for those drugs with a narrow therapeutic range.

Notterman DA (23) reported on an infant in whom use of a crushed tablet of isoniazid administered in apple sauce was associated with low plasma isoniazid levels and treatment failure. Oral administration of the parenteral solution of isoniazid in apple juice produced a higher isoniazid concentration and the child improved clinically. Subsequent pharmacokinetic studies comparing (a) an isoniazid tablet crushed and mixed with apple sauce (b) parenteral isoniazid mixed with apple juice (c) a commercially available syrup containing isoniazid and pyridoxine showed the latter to produce the highest peak concentrations of isoniazid. The authors suggest impaired GI absorption of crushed isoniazid tablets administered with food may have been the cause of the lower than expected isoniazid concentrations.

In their study, Ansah et al (24) reported improved compliance in children in rural Africa who were treated with chloroquine tablets or segments (crushed and mixed with sugar or honey) rather than chloroquine syrup. They felt that children treated with syrup could be underdosed because of the use of inadequate measuring devices by their parents. In response to this article however, Standing and Wong (25) comment that there was no description in the article if the tablets could be accurately segmented and there was no supporting data to show that the crushed tablets delivered the drug adequately.

Other important factors that must be considered before deciding whether to crush tablets or open capsules include:

- medicines which are coated to prevent absorption in the stomach will be broken down in the stomach causing irritation or failure to reach the intended site of action
- crushing of medicines which are coated to disguise the flavour of the drug may result in the patient having to take an unpalatable powder which can reduce compliance
- exposure pharmacist, patient or carers to skin contact or inhalation of potentially noxious powder

Despite these potential problems, the practice of crushing tablets or opening capsules is relatively common practice and there is some guidance in adult patients which can possibly be translated to the paediatric population. However, this adult guidance is designed for whole doses i.e. crushing and administering the entire tablet or using the entire contents of a capsule rather than taking a proportion as is often necessary in children. Useful adult reference sources include: UKMI academic detail aid for prescribers – Choosing medicines for patients unable to take solid oral dosage forms (26); Consensus Guidelines on the medication management of adults with swallowing difficulties (Rosemont) (27), The Handbook of Administration of Drugs by Enteral Feeding Tubes (28) the NEWT Guidelines (29), Guidance for the use of unlicensed medicines in paediatric patients (Rosemont) (30) and the Handbook of Extemporaneous Preparation, 2010 (15), provide useful general guidance. They also consider the legal implications of altering a solid-dose oral formulation.

As there is not likely to be any data on the stability of the powder obtained from crushing a tablet or opening a capsule, this practice should be done immediately prior to administration.

There are also some general articles (31, 32, 33, 34, 35) which discuss which solid oral dosage forms may be crushed to facilitate swallowing. In general, enteric-coated, buccal, sublingual and most extended-release formulations should not be crushed.
Modified release – medicine is designed to be released over a prolonged period. If the mechanism for the slow release is damaged, the patient will receive the full dose quicker than expected (increased risk of toxicity) and subsequently little or no dose for a period of time (decreased efficacy).

Enteric coated – if the coating is present to protect the stomach, consider adding a suitable gastro-protective product. If the coating is designed to deliver drug beyond the stomach, crushing may result in the medicine not reaching the intended target.

Film or sugar coated – disruption may result in rapid degradation of drug, poor tasting medicine and possible skin irritation of the patient/carer.

Conclusion

Crushing tablets or segments of tablets or opening capsules and administering the powder contents appears to be common for those with swallowing difficulties and some advice is available. However, this process may affect bioavailability the importance of which should be assessed for each drug.

In addition, it may also be possible to withdraw the liquid contents from capsules e.g. nifedipine but the volume contained within the capsules is known to vary between different generic brands. It is very difficult in practice to withdraw this viscous liquid and to ensure an accurate volume is given.

4.6.3 Dispersing capsule contents or crushed tablets in water, liquid or soft food

To aid administration, the capsule contents or crushed tablets described in (ii) may need to be dispersed in water, other liquid or soft food. All the potential risks associated with crushing tablets will obviously apply also in this situation and in addition, there are further issues which need to be considered.

If a tablet, tablet segment or capsule content disperses in water, it can be dispersed in a small volume and the dose given when a suspension is formed (36, 15). When dispersing tablets, the dose should be prepared and administered immediately as stability cannot be guaranteed. To ensure the required dose is taken, it is important that all the liquid vehicle used is administered.

It is more difficult to ensure dose accuracy in children, when the required doses are frequently fractions of the lowest available tablet strength. If a tablet disperses readily and the drug is soluble, dispersing the tablet in a known volume of water and taking the required proportion (accurately measured with an oral syringe) allows a relatively accurate dose to be administered (e.g. stavudine, oseltamivir).

However, if the drug is poorly soluble, this practice presents a significant risk of dose inaccuracy (12, 15, 37). As water has no suspending properties, dispersal of insoluble drug can result in aggregation and sedimentation of the drug and despite mixing/shaking well immediately before the required volume is withdrawn, uniform dispersal of the drug cannot be guaranteed. In addition, there is no consistency of dose which could vary on each occasion.

Although much work has been done on the stability of some drugs (e.g. captopril (38)) dispersed in water, generally this data is not available. When a dosage form is altered, the stability of the drug may be affected and, as a general rule, the rate of degradation of a drug increases once it is dissolved or dispersed (39). The preparation and administration of doses from dispersing tablets or capsule contents in water should be done immediately prior to administration. If only part of the volume is required, any remaining must be discarded and not used for any subsequent doses.
Conclusion

There is limited information to support the practice of dispersing crushed tablets or capsule contents in water or soft food and evidence is based largely on anecdotal reports and clinical practice. For drugs known to be soluble in the volume of water used for dispersion, this may allow an accurate dose to be administered if a proportion of the solution is calculated and measured accurately. For drugs that are poorly soluble it is preferable to segment the tablet and then disperse in liquid for administration. The availability of orodispensible tablets or lyophilised wafers would offer considerable benefits. These formulations are placed in the mouth where they disperse or ‘melt’ on the tongue. They are easy to administer, do not require water and as dispersion is generally rapid, it is difficult for a child to spit out. A range of dosages appropriate for use in younger children may be needed. Another option is the development of similar solid dose formulations that can be used to prepare an oral liquid at the time of administration possibly even using breast milk to make this an option even in the very youngest babies.

4.6.4 Segmenting suppositories

The rectal route of administration is an established route of drug administration and can be used to achieve either local or systemic effects. Assuming a uniform distribution of the active substance in the suppository matrix, it may be possible to halve suppositories longitudinally to achieve a proportion of a dose. Again, there is unlikely to be any accuracy or stability data for such a practice and the resulting shape may not be optimal for rectal insertion. Compliance with the rectal route may be lower than for oral dosage forms as the rectal route is poorly accepted by patients and caregivers in certain countries and cultures [40].

A study by Kim et al, [41] looked at the accuracy of alteration of paracetamol suppositories. Whilst the investigation revealed uniform distribution of paracetamol there was poor accuracy in achieving the target dose. The authors suggest using only intact suppositories for improved accuracy.

Conclusion

There is little information on segmenting suppositories and they are known to have variability in uniformity of content especially if produced extemporaneously. The pharmacist should consider recasting suppositories in smaller moulds to get smaller doses or if segmenting is essential to consider the therapeutic index of the drug and the consequences of over or under dosing.

4.6.5 Powders / small strength capsules [extemp dispensing rather than manipulation]

Fractional doses can be prepared by repacking dose aliquots of powdered tablets or capsule contents. Some doses may need to be mixed with a diluent such as starch or lactose before repacking into powder papers or empty capsules. In general, if stored under suitable conditions away from moisture, these should have greater stability than oral liquids but are much more time consuming to prepare. In addition, uniform drug distribution must be ensured to allow for accurate dosing. The pharmacokinetics of the drug may be considerably altered and there is little scope for flexibility of the dosage without preparation of a further batch of powders. [14, 42]

Conclusion

Use of powders is a common practice in some countries (e.g. European countries such as Finland and Italy [7] and Japan) but in general there is little information on any effects on bioavailability and or stability of the active ingredient.
5. Extemporaneous dispensing

There will however remain circumstances in which there is no licensed medicine, ‘special’ or suitable manipulation of a licensed preparation that can meet the needs of a patient or group of patients. In these circumstances it can be necessary for the pharmacist to extemporaneously prepare a medicine.

5.1 Dangers

Extemporaneous preparation remains one of the highest risk preparative activities carried out in pharmacy as the risks of unlicensed medicines are combined with the inherent risks associated with the compounding of an extemporaneous formulation (15).

5.2 Problems

There appears to be little consistency regarding the practice of compounding within and across countries and continents. Certainly in the UK, the same prescription could be prepared according to very different and often locally developed monographs because of the lack of a national source of compounding information. Standardising compounding practices and harmonising formulations and information on stability would go a long way to guaranteeing the quality, safety and efficacy of compounded preparations.

There are differences in the approach to compounding across Europe and, for example, Carvalho et al (43) report on significant differences in the concept, definition, type and legal status of compounded products in Portugal and the UK. Extemporaneous compounding is a far more common practice in European countries such as Portugal, Spain and Germany than in the UK where community pharmacists primarily dispense ‘specials’ instead of extemporaneously prepared medicines. In addition, Portuguese and German pharmacists have official formularies for compounded preparations so there is more standardisation of prescriptions.

Brion et al, (7) conducted a questionnaire survey of 41 hospital pharmacists in 18 European countries to evaluate methods of preparation of oral medicines when drugs prescribed are unlicensed or off-label and to determine whether such extemporaneously prepared medicines were available as suitable, authorised products in other countries. Information was requested on the most frequent extemporaneously prepared oral liquid, powder and capsule and on their formulation and stability. 21 questionnaires from 16 countries were returned and showed the methods of preparation to vary in different countries with liquids favoured in England and Sweden, powders in Finland and Italy and capsules in France and Spain. In addition, many of the extemporaneous preparations were available as suitable authorized paediatric medicines in other countries. It was also noted that the quality of information on formulation and stability was limited and there were concerns about the availability and quality of chemical ingredients.

5.3 Guidance / Standards

From a general internet search and personal communications, we identified some examples of national guidance/standards for extemporaneous compounding and these are listed in appendix 3.

The level and detail of information included varies considerably between countries and standards in developing countries will be limited by lack of resources (including the availability of active ingredients and even water or equipment), trained personnel and facilities. However, to varying degrees, the standards/guidance identified does tend to include advice on expected standards for the following aspects of extemporaneous compounding:
- competency of staff involved in compounding
- formulation and stability (both physical and microbiological) stability
- source and quality of ingredients
- site, facilities and equipment
- quality assurance
- effective documentation
- containers and labelling
- recall procedure

5.4 competency of staff involved in compounding

In the UK, the RPSGB and the BP specify that ‘the manufacture or preparation of unlicensed medicines should be in accordance with appropriate current standards of GMP and, where applicable, good dispensing practice’ and that ‘the manufacture or preparation of unlicensed medicines should only be undertaken by competent staff within suitable facilities’. Similar requirements for competency of the pharmacist and any technical staff are expected by standards stipulated in the USP and by the Pharmaceutical Society of Australia. All training activities are covered by standard operating procedures and fully documented.

In developing countries – conditions of pharmacy practice vary widely from country to country and even between different sectors or areas within a country (e.g. there could be a significant difference between the health services available in urban and rural areas in developing countries). In many cases this difference is due to an insufficient number of pharmacists and can mean trained support personnel such as technicians having to work alone.

The WHOSIS database in 2004 (44) identified that only ten African countries had more than 10 pharmacists per 100,000 population at that time. Whilst the FIP and WHO have encouraged national pharmaceutical associations in individual countries to decide what can be achieved in terms of GPP, in many developing countries, national organisations are either non-existent or else too small to carry out such an exercise.

5.5 formulation and stability

Much has been written on formulation and stability of extemporaneous preparations (See appendix 4). Where there is a need to undertake extemporaneous preparation, the pharmacist must choose an appropriate formula. Ideally all formulae used should be validated and have supporting data (15). However, due to the paucity of data, it is often likely that a fully validated formula will not be available and in this instance, advice may be available from NHS and commercial ‘specials’ manufacturers, QC departments and medicines information departments. When supporting data are incomplete, the formulation should be kept as simple as possible with a short shelf life until further information is available. In all the standards/guidance identified and included in appendix 3 the guidance states that a trained person (ideally a pharmacist) must be satisfied as to the safety and appropriateness of the formulation. This will involve checks on all calculations and measurements involved.

Calculation errors pose a great risk of causing serious patient harm (15) and the greater the complexity of calculation required, the higher the risk of an error. Formulations should be kept as simple as possible and all calculations should be independently checked and documented on a work sheet.

Use of the wrong strength of chloroform water in a formulation for peppermint water resulted in the death of a child in the UK and highlighted the risks both of using toxic ingredients and of calculation errors (45)
With regard to oral liquid formulations, insoluble drugs can often be suspended in universally available suspending agents for a short time with little or no significant chemical degradation (15). However, most published formulations are in commercially available bases such as Ora-Plus and Ora-Sweet which are not generally available especially in developing countries.

Extemporaneous compounding without suspending agents can cause patient harm. A recent report in the UK describes the extemporaneous dispensing of a clobazam liquid in which the clobazam was not effectively suspended and so caked on the bottom of the bottle meaning the child did not receive an adequate dose and experienced an increase in his number of seizures (30).

A further issue to be considered in extemporaneous formulation is the need for preservatives and excipients and any potential harm their use may cause to children.

Excipients are considered to be therapeutically inactive components of a medicine and have many important functions including use as diluents, wetting agents, solvents, fillers, preservatives, absorption enhancers, sweeteners, stabilisers and colouring and flavouring agents. Administration of pharmaceutical excipients can produce adverse effects especially in neonates. However, the exclusion of these agents (notably when used as a co-solvent, stabiliser or preservative) may lead to erratic dosing, chemical degradation and microbial growth.

There are a number of reviews on the risks and benefits of excipients in extemporaneous formulations (15, 40, 46, 47, 48, 49) and these are useful for further information. In general however, whilst we know which are the potentially problematic excipients, safe limits of these in babies, infants and children have not been established. This re-enforces the need for development of global level extemporaneous formulations with minimal excipients that can be used universally.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Potential risks</th>
<th>Suggested maximum daily intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzyl alcohol</td>
<td>Metabolic acidosis; respiratory and CNS depression</td>
<td>WHO arbitrary limit: 5mg/kg/DAY in adults.</td>
</tr>
<tr>
<td>Ethanol</td>
<td>CNS depression and respiratory and cardiovascular toxicity at high concentrations</td>
<td>American Academy of Pediatrics: arbitrary limit for blood ethanol concentration of 25mg per 100ml following a SINGLE dose. Safe limits following chronic dosing unknown</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>CNS toxicity and hyperosmolality</td>
<td>WHO arbitrary limit in adults: 25mg/kg/DAY</td>
</tr>
<tr>
<td>Parabens</td>
<td>Can cause hypersensitivity</td>
<td>No information</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>Osmotic diarrhoea</td>
<td>No information</td>
</tr>
<tr>
<td>Sweeteners</td>
<td>Sucrose/dextrose – dental caries</td>
<td>No information</td>
</tr>
<tr>
<td></td>
<td>Aspartame – harmful in PKU patients</td>
<td></td>
</tr>
<tr>
<td>Glycerol</td>
<td>High concentrations and volumes may cause mucositis or</td>
<td>No information</td>
</tr>
</tbody>
</table>
5.6 source and quality of ingredients

It is the responsibility of the trained personnel (ideally a pharmacist) to ensure ingredients must be of an acceptable pharmaceutical quality. Pharmacists must pay particular attention to substances which may be hazardous and require special handling techniques.

The ideal scenario is the availability of ingredients of pharmaceutical quality (e.g. in the UK to meet with the specific requirements of the British Pharmacopoeia if a monograph is available, in the US ingredients that comply with the USP). In any situation, steps should be taken to ensure satisfactory quality of any substance used in extemporaneous compounding. It must be acknowledged however that this is a particular problem in developing countries where even water of a suitable quality might not be available.

When tablets are used as a starting material for making a suspension, care should be taken to ensure they are ground to a fine uniform powder. A lack of uniformity in particle size may have a detrimental effect on dose accuracy.

5.7 site, facilities and equipment

All standards/guidance identified advises that the site used should be fit for purpose and protected from possible sources of contamination. Equipment should be of appropriate design and size and be inspected, maintained, cleaned and validated at appropriate intervals to ensure accuracy and reliability of performance. The expected standards for areas designated for compounding vary considerably between developed and developing countries and within rural and urban areas of developing countries. Basic requirements are a clean and tidy area, adequate light, protection from exposure to excessive heat and light (with a fridge if necessary) and appropriate equipment.

In the developed countries, standards require potable water to be supplied for hand and equipment washing and purified water must be used for compounding nonsterile drug preparations and for rinsing equipment and utensils. However, this is a particular problem in developing countries where water of a suitable quality might not be available.

5.8 quality assurance

Ideally, the pharmacist (or trained personnel) should prepare and dispense compounded products in a manner that ensures product quality, safety and efficacy and in accordance with good compounding practices, official standards and relevant scientific data and information (if such information exists). US and UK standards advise that critical processes are validated to ensure that procedures, when used, will consistently result in the expected qualities in the finished preparation. Appropriate stability evaluation is performed or determined from the literature to establish reliable expiry data to ensure that the finished preparations have their expected potency, purity, quality and characteristics, at least until the labelled expiry date. There should be assurance that processes are always carried out as intended or specified and are under control.

5.90 effective documentation

The records must include the formula, the ingredients and the quantities used, their source, batch number and expiry date. Where the preparation is dispensed in response to a prescription, the
records must also include the patient’s and prescription details and the date of dispensing. A record must be kept of personnel involved including the identity of the pharmacist taking overall responsibility.

A further objective of the documentation is to allow another compounder to reproduce the identical prescription at a future date. This provides a consistent source document for preparing the formulation and the compounding record documents the actual ingredients in the preparation and the person responsible for the activity.

5.10 use of suitable containers and correct labelling

Primary packaging of the product must be fit for purpose and adequately protect the product from the environment whilst being compatible with the product.

Ideally the product must be labelled with the necessary particulars, including any special requirements for the safe handling or storage of the product.

- common name of product
- statement of the active ingredients expressed qualitatively and quantitatively per dosage unit or for a given volume or weight
- dose and route of administration
- contents of the container by weight, volume or number of doses
- expiry date
- batch number
- name and address of patient

However in some rural areas of developing countries, many pharmacies do not have containers and patients may bring their own containers with no labelling available.

5.12 documented procedure for complaints and recalls of dispensed compounded products

If product deficiencies considered potentially harmful to health are identified, a product recall should be initiated immediately. A written procedure for a recall should be in place (15)

Conclusions

Extemporaneous preparation poses a high risk to patient safety and is generally subject to low levels of quality assurance. Adherence to standards for extemporaneous dispensing is necessary to ensure safe preparation of good quality products. Standardising current products and formulae for which there is good quality efficacy and stability data and promoting this information is essential to improve current practice.

6. improving the situation

6.1 US and EU legislation

European regulation No 1901/2006 and US .......... aims to increase the availability of well studied medicines intended to be used in children, to make information on these medicines widely available and to encourage high-quality, ethical paediatric research to produce this information. Through establishment of a framework of rewards, incentives and obligations for pharmaceutical companies, the legislation aims to encourage the development of medicines appropriately tested, authorised and formulated for use in children

6.3 **EMEA reflection paper** – Formulations of Choice for the Paediatric Population

6.4 **National Paediatric Research Networks** – e.g. MCRN in the UK; PAED-Net in Germany; NIH in the US; TEDDY in Europe to facilitate the conduct of randomised trials and other well designed studies including improvement in extemporaneous formulations

- Options
  - Authorised dosage form as starting point
- Ingredients
- Information on formulations

7. **Current research/relevant ongoing work**
Appendix 1. Methodology

As well as using personal reference collections, NHS Evidence, Evidence Based Reviews (incl Bandolier, Cochrane, DARE, HTA Database), Medline, Embase and International Pharmacy Abstracts were searched.

MEDLINE

Search History:

1. MEDLINE; exp DRUG COMPOUNDING/; 10276 results.
2. MEDLINE; exp GUIDELINE/ OR exp PRACTICE GUIDELINE/; 20180 results.
3. MEDLINE; exp REFERENCE STANDARDS/; 27261 results.
4. MEDLINE; 2 OR 3; 47255 results.
5. MEDLINE; 1 AND 4; 65 results.
6. MEDLINE; (tablet AND manipulation).af; 35 results.
7. MEDLINE; (tablet AND segment$).af; 124 results.
8. MEDLINE; (crush$ AND tablets).af; 381 results.
9. MEDLINE; (openi$ AND capsule$).af; 596 results.
10. MEDLINE; (open$ AND capsule$).af; 2709 results.
11. MEDLINE; 6 OR 7 OR 8 OR 9 OR 10; 3237 results.
12. MEDLINE; (cut$ AND tablet$).af; 468 results.
14. MEDLINE; (dose AND banding).af; 351 results.
15. MEDLINE; 13 OR 14; 413 results.
16. MEDLINE; exp DRUG ADMINISTRATION SCHEDULE/; 73785 results.
17. MEDLINE; exp PHARMACOKINETICS/; 131622 results.
18. MEDLINE; 16 AND 17; 2670 results.
19. MEDLINE; 18 [Limit to: (Age Groups All Child 0 to 18 years)]; 453 results.
20. MEDLINE; (therapeutic AND index).af; 20060 results.
21. MEDLINE; 16 AND 20; 739 results.
22. MEDLINE; 21 [Limit to: (Age Groups All Child 0 to 18 years)]; 131 results.
23. MEDLINE; 1 [Limit to: (Age Groups All Child 0 to 18 years)]; 255 results.
24. MEDLINE; (segment$ AND suppository).af [Limit to: (Age Groups All Child 0 to 18 years)]; 1 results.

25. MEDLINE; (segment$ AND suppository).ti,ab; 10 results.

26. MEDLINE; (dose AND manipulation).af; 2066 results.

**Search History:**

1. EMBASE; exp DRUG FORMULATION/; 82226 results.

2. EMBASE; 1 [Limit to: (Human Age Groups Child unspecified age)]; 1954 results.

3. EMBASE; (extemporaneous AND formulation).af [Limit to: (Human Age Groups Child unspecified age)]; 26 results.

4. EMBASE; (extemporaneous AND formulation).af; 171 results.

5. EMBASE; (tablet AND crush$).af; 555 results.

6. EMBASE; (tablet AND cut$).af; 298 results.

7. EMBASE; (tablet AND split$).af; 176 results.

8. EMBASE; (tablet AND segment$).af; 201 results.

9. EMBASE; 5 OR 6 OR 7; 1006 results.

10. EMBASE; 8 OR 9; 1197 results.

11. EMBASE; (open AND capsule).af; 1859 results.

12. EMBASE; (suppository AND cut).af; 10 results.

13. EMBASE; (suppository AND segment$).af; 22 results.

14. EMBASE; (injection AND oral$).af; 21943 results.

15. EMBASE; (therapeutic AND substitution).af; 0 results.

16. EMBASE; (dose AND banding).af; 411 results.

17. EMBASE; (dose AND manipulation).af; 2536 results.

IPA – drug compounding (includes drug preparations, drug preparation, preparations drug, compounding, drug); tablet crushing, drug formulations, dose manipulation, segment suppository, open capsules

Internet search – extemporaneous/compounding/manipulation/goodpractice

E-drug enquiry

Personal contacts
Andy Gray, South Africa
Sean Turner, Adelaide Children’s Hospital
David Wright, School of Pharmacy UEA
Regis Vaillancourt, Canada
Atieno Ojoo, UNICEF – DW to do.
Others – AJN in hand.
Appendix 2. References

8. United States Pharmacopoeia
9. www.unicef.org
11. need reference
13. Kairuz T. Extemporaneous compounding in a sample of New Zealand Hospitals: a retrospective survey; 120(1251): online
18. USP-NF. General Chapter 905: Uniformity of Dose Units


26. UKMI. Academic detail aid for prescribers – choosing medicines for patients unable to take solid oral dosage forms. January 2010

27. Wright D et al. Consensus guideline on the medication management of adults with swallowing difficulties. Sponsored by Rosemont Pharmaceuticals


31. McPherson ML. Don’t crush that tablet. American Pharmacy, 1994; NS34: 57-58


38. Lowey A and Jackson M. How to ensure the quality and safety of unlicensed oral medicines. PJ, 2008

39. Hanson G. Bespoke pharmacy: tailoring medicines to the needs of patients – the pharmacy production unit’s role. Hospital Pharmacist, 2003; 10: 155-159


46. Nahata MC. Safety of ‘inert’ additives or excipients in paediatric medicines. ADCH (F+N, 2009; 94: F392-93

47. Formulation in Pharmacy Practice. 2nd Edition

48. EMEA. Committee for Medicinal Products for Human Use. Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product. June 2007

# Appendix 3. Standards for Extemporaneous Compounding / Formulation

**GUIDANCE / STANDARDS ON PREPARATION OF EXTEMPORANEOUS FORMULATIONS**

<table>
<thead>
<tr>
<th>Source</th>
<th>Guidance / Standards</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK</strong></td>
<td></td>
</tr>
<tr>
<td>RPSGB</td>
<td>Standards for Extemporaneous Preparation / Compounding 2000. Not great detail</td>
</tr>
<tr>
<td>British Pharmacopoeia 2011 Online</td>
<td>Unlicensed Medicines including Standards for Preparation and Manufacture of Unlicensed Medicines</td>
</tr>
<tr>
<td>UK Working Party</td>
<td>Guide to the Preparation of Non Sterile Extemporaneous Products, 2002. Comprehensive document to be used as a guide to raise awareness of the extemporaneous dispensing process and raise awareness of the principles of clinical governance</td>
</tr>
<tr>
<td><strong>EUROPE</strong></td>
<td></td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td></td>
</tr>
<tr>
<td>US Pharmacopoeia USP29</td>
<td>Chapter 1075  Good Compounding Practices</td>
</tr>
<tr>
<td>US Pharmacopoeia USP29</td>
<td>Chapter 795 Pharmaceutical Compounding – Nonsterile Preparations</td>
</tr>
<tr>
<td>US Pharmacopoeia USP 29</td>
<td>Chapter 797 Pharmaceutical Compounding – Sterile Preparations</td>
</tr>
<tr>
<td>US Pharmacopoeia USP29</td>
<td>Chapter 1160 Pharmaceutical Calculations in Prescription Compounding</td>
</tr>
<tr>
<td>US Pharmacopoeia USP 29</td>
<td>Chapter 1163 Quality Assurance in Pharmaceutical Compounding</td>
</tr>
<tr>
<td><strong>AUSTRALIA</strong></td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical Society of Australia.</td>
<td>Standard 10: Compounding (also known as Extemporaneous Dispensing).</td>
</tr>
<tr>
<td>Professional Practice Standards</td>
<td>Version 4, 2010</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Pharmaceutical Society of Australia</td>
<td>National Competency Standards Framework for Pharmacists in Australia, 2010</td>
</tr>
<tr>
<td>Oceania Health</td>
<td>Review of the need for further regulation of extemporaneous compounding. January 2005</td>
</tr>
</tbody>
</table>

**SULTAN QABOOS**

| Sultan Qaboos University Hospital. Personal Communication | Have standard operating procedures on extemporaneous compounding. No formal written guidelines or standards on manipulation of dosage forms. Clinical pharmacists advise and guide clinicians on rounding doses to avoid extemporaneous preparations. Not aware that guidelines exist in any other Gulf countries |

**ZIMBABWE**

| Personal Communication | No specific national or local instructions or guidance on manipulation of doses or extemporaneous preparation in Zimbabwe from regulators or from their pharmaceutical society. Rely on international literature where available. Some clinics may have scant local standard operating procedures developed over 10 years ago when there was more skilled workforce available |

**SWITZERLAND**

| Personal Communication | Follow Good Manufacturing Practice in the Pharmacopoeia Helvetica which is obligatory for preparing small amounts of medication in hospital pharmacies. A guidance on pharmacy preparations is in preparation. Presently hospitals have their own guidance documents to prepare preparations, especially paediatric dosage forms. Generally extemporaneous preparations are avoided if an appropriate dosage form is available |

**GERMANY**

| Personal Communication | Have a compounding book ‘Neues Rezeptur-Formularium (NRF)’ [www.deutscher-apotheker-verlag.de/bereiche/pharmazie/armebeucher-und-kommentare/view/titel/797.html](http://www.deutscher-apotheker-verlag.de/bereiche/pharmazie/armebeucher-und-kommentare/view/titel/797.html) which has some specific formulations and also general monographs on capsules etc. 312 drug formulations are licensed as ‘Standardzulassung’ ie have standard marketing authorization with some old drugs and particularly herbal plant mixtures. Very little for paediatrics |

| International Journal of Pharmaceutical Compounding, 2008; | Federal law (primarily the Arzneimittelgesetz) and subordinate federal directives (primarily the Apothekenbetriebsordnung) regulate anything concerning the technical aspects of and structural requirements for a |
compounding pharmacy, such as the contents of the analytical laboratory, equipment, hygiene, storage and preparation areas and the qualifications of personnel.

Any pharmaceutical dosage form can be compounded if the quality of the compounded preparation can be guaranteed.

Expiry dates for standardized formulas are provided in the Neues Rezeptur-Formularium (NRF)

Official monographs on medicinal products for human and veterinary use have been established. These monographs are considered licenses (Standardzulassungen) that are valid for compounding in German pharmacies

**ITALY**

<table>
<thead>
<tr>
<th>Personal Communication</th>
<th>Italian Society of Hospital Pharmacy has recently produced a manual of guidelines covering extemporaneous preparations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maurizio Bonati</td>
<td>Italian regulations allow the extemporaneous preparation of drugs only when they are not available on the domestic market in either the correct dosage form or because of drug substance inaccessibility. Pharmacists are required to evaluate the following before authorizing the prescription and are also required to define the procedures to be followed: drug unavailability on the market; therapeutic alternatives in conjunction with the prescriber; prescription accuracy and compliance with maximum dose allowed in the Italian Pharmacopoeia; preparation feasibility with respect to the prescription and the possible use of excipients if allergies are suspected; benefit/risk ratio of use in clinical practice.</td>
</tr>
<tr>
<td>Chiara Tibaldo</td>
<td></td>
</tr>
<tr>
<td>Annalisa Campomori</td>
<td></td>
</tr>
</tbody>
</table>

Physicians give pharmacists all relevant information regarding their patients including allergies. The hospital pharmacist then prepares a working scheme for the technician working in the compounding lab. Complete guidelines for every pharmaceutical preparation are available to pharmacists and technicians for the correct and safe production of formulations.

**CANADA**

<table>
<thead>
<tr>
<th>Health Products and Food Branch Inspectorate, Health Canada</th>
<th>Policy on Manufacturing and Compounding Drug Products in Canada. POL-0051, January 26th 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Society of Hospital Pharmacists</td>
<td>Nonsterile Compounding: Guidelines for Healthcare Facility Pharmacies, 1992</td>
</tr>
<tr>
<td>Canadian Society of Hospital Pharmacists</td>
<td>Repackaging: Guidelines for Healthcare Facilities, 1998</td>
</tr>
<tr>
<td>Boggio L. Chair, Working Group to Examine Pharmacy</td>
<td>Guidelines for Compounding Preparations. Pharmacy Connection, July/August 2006: 18-21</td>
</tr>
</tbody>
</table>
### BRAZIL

**Personal Communication**

ANVISA have a regulation (RDC 67/2007) that includes an annex VI that describes the conditions needed to prepare unitary doses including manipulation of dosage forms and other procedures needed to prepare medicines for children, for administration via nasogastric tubes, for extemporaneous formulations and criteria for manipulation.

Some Brazilian public and private institutions prepare their own basic guidelines about extemporaneous formulations.

### ESTONIA

**Personal Communication**

No standards or guidelines for extemporaneous compounding in Estonia at present. The Estonian Hospital Pharmacists Association has started this summer, 2010, to collect the extemporaneous prescriptions from different Estonian hospital pharmacies and are analyzing the data to prepare an extemporaneous drugs formulary for the hospitals. This will include extemporaneous compounding for children.

### POLAND

**Personal Communication**

No standards or guidelines for manipulation of doses or for extemporaneous compounding.

Drug compounding used to be taught well at the Universities and at schools for technicians. The textbooks are available but are not treated as official guidance. Recently, teaching of compounding is less and less professional and there is great need for standards. Some work on preparations for the National Pharmacopoeia has been started.

### HOLLAND

**Personal Communication**

Extemporaneous compounding formularium KNMP LNA

Handbook on parenteral drugs (KNMP)

Scientific body (WINAP)

KNMP due to publish a handbook on manipulation of oral dosage forms

www.knmp.ml

### SOUTH AFRICA

**Personal Communication**

In South Africa the right of pharmacists to compound is entrenched in the Medicines Act

# Developing Countries

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
</tr>
</thead>
</table>

# New Zealand

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
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</thead>
</table>

# Ethiopia

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Administration and Control Authority of Ethiopia</td>
<td>Standards for the Establishment and Practice of Pharmaceutical Compounding Laboratory, 2002</td>
</tr>
</tbody>
</table>

# Mexico

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors advise the Mexican Pharmacopoeia, which contains specifications, tolerances and procedures to assure the official Mexican requirements for quality of drugs prepared in the country, should be used</td>
<td></td>
</tr>
</tbody>
</table>

# Argentina

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Journal of Pharmaceutical Compounding, 2008; 12(2): 105</td>
<td>Practice of compounding is regulated and restrictions are imposed by the Argentina Health Department. However, Argentina has few established regulations to guide the daily compounding practices and the guidelines on which pharmacies are regulated are based on outdated legislation</td>
</tr>
</tbody>
</table>

# Belgium

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Journal of Pharmaceutical Compounding, 2008; 12(2): 106</td>
<td>Practice of compounding is regulated by the Ministry of Health. The compounding of pharmaceuticals, including nonprescription (over-the-counter) medicines is permitted in Belgium and pharmacists are allowed to compound every dosage form as long as ‘forbidden’ active ingredients are not used. However few pharmacists have a great interest in compounding and those that do encounter problems in complying with</td>
</tr>
</tbody>
</table>
### COLOMBIA

Compounding of both nonsterile and sterile preparations is regulated by the INVIMA Drug and Food Surveillance National Institute. A new law based on very stringent European (Spanish) and American standards has been proposed.

Orientation to the use of manufactured pharmaceuticals is one of the main reasons why compounding in Colombia has not developed substantially.

### PUERTO RICO

Compounding is regulated by the Department of Health of Puerto Rico through the Division of Drugs and Pharmacies in the Assistant Ministry of Regulation and Accreditation of Health Facilities Act No 247, 2004, which is known as the Pharmacy Act of Puerto Rico and created to enable more effective monitoring. The Act does not provide clear guidance for the practice of compounding.

At the present, the regulations are under development and will stipulate compliance with USP Chapter 795 for nonsterile formulations and USP Chapter 797 for sterile formulations.

### SPAIN


Compounding activities, laboratories and equipment must comply with RD175/2001.

### NEPAL


### SUDAN

Extemporaneous Compounding in Specialized Pharmaceutical Laboratories (ECSPL) Guidelines

Follows USP standards.
Appendix 4

Formulation and stability


Formulation in Pharmacy Practice, 2nd Edition


Paddock Laboratories www.paddocklabs.com
Appendix 5

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Books


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Problems with extemporaneous preparation/manipulations

Mulla H et al. Variations in captopril formulations used to treat children with heart failure: a survey in the UK. ADCH, 2007; 92: 409-411


McPherson ML. Don’t crush that tablet. Am Pharmacy, 1994; N534: S7-S8

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Mitchell J. Oral dosage forms that should not be crushed or chewed. Hosp Pharmacist, 2002; 37(2): 213-14


Bronzetti G et al. Solution to a crushing dosage problem? Pediatrics, 2001; 113: 1468


Rosenberg JM et al. Weight variability of pharmacist dispensed split tablets. J Am Pharm Assoc, 2002; 42(2): 200-05


Toedter Williams N. Medication administration through enteral feeding tubes. Am J Health System Pharmacy, 2008; 65: 2347-57


**Regulatory guidelines/reflection papers**

EMEA Guidance – Guideline on the investigation of medicinal products in the term and preterm neonate


EMEA. Committee for Medicinal Products for Human Use (CHMP). Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product. June 2007


MHRA advice 2010 – Information for wholesale dealers and manufacturers: advertising of unlicensed medicines

MHRA / DOH Strategy on Medicines for Children. July 2004

MHRA. The supply of unlicensed relevant medicinal products for individual patients. Guidance Note No 14. Jan 2008


Better Medicines for Children: EU Paediatric Regulation 2007

**Excipients**

Nahata MC. Safety of ‘inert’ additives or excipients in paediatric medicines. ADCH(F+N), 2009; 84: F392-F393


Whittaker A et al. Toxic additives in medication for preterm infants. ADCH (F+N), 2009; 94: F236-F240


AAP Committee on Drugs. ‘inactive’ ingredients in pharmaceutical products: update. Pediatrics, 1997; 99: 268-278


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WHO. Medicines for Children Factsheet No 341. June 2010


Paediatric Regulators Network Meeting. Report to WHO concerning international guidelines for paediatric medicines. Feb 2010

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Caroline le Barbier, EMEA, Human Unit, Quality Sector. Age-appropriate formulation and paediatric investigation plans – a quality point of view. Formulating better medicines for children. Presentation. RPSGB March 2009


Beaney AM. Supply of and Standards for ‘Specials’ and extemporaneously prepared medicines for NHS patients in the 21st century. Presentation. RPSGB, March 2009

Reviews


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**Palatability**


Standards for extemporaneous preparation

Hanson G. Bespoke pharmacy: tailoring medicines to the needs of patients – the pharmacy production units role. Hospital Pharmacist, 2003; 10: 155-159


Donnelly R et al. Is extemporaneous dispensing really in the best interest of patients? PJ, 2008; 280: 251-254


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RPSGB. Developing and implementing SOPs for dispensing. Nov 2007

USP – Pharmaceutical Compounding. Non-sterile preparations. Chapter 795

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Lowey A and Jackson M. How to ensure the quality and safety of unlicensed oral medicines. PJ, 2008


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Wright D et al. Consensus guideline on the medication management of adults with swallowing difficulties. Supported by Rosemont

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Sudan National Medicines and Poisons Board. Extemporaneous Compounding in Specialized Pharmaceutical Laboratories Guidelines


WHO Expert Committee on Specifications for Pharmaceutical Preparations, 957, 47th report 2010

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Breitkreutz J. Novel drug formulations for children. Presentation, July 2010


McElhiney LF. Information resources and software for the hospital compounding pharmacist. Int J Pharm Compounding, 2007; 11(1): 36-41


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Pandit S et al. Inappropriate oral formulations and information in paediatric trials. ADCH, 2010; 95: 754-756

Candish CA et al. Do pharmacists extemporaneously dispense or do they use specials manufacturers? Int J Pharmacy Practice, 2003; 11: R47

Gross Z. Why specials manufacturing units are needed now as much as they ever were. PJ, 2005; 275: 743-746


Rennison SM, Portlock JC. Is it time to stop dispensing extemporaneously in hospital pharmacy? Int J Pharm Pract 2003; 11: R68
Appendix X  Glossary

Age-appropriate formulation/dosage form

A dosage form considered (by healthcare professionals and carers) suitable for the age and ability of the child.

Compounding

The US Pharmacopoeia (8) defines compounding as ‘preparation of a “customized” prescription drug product for a patient whose physician has determined that his or her medical needs cannot be met by a commercially manufactured prescription drug product (for example, a pediatric patient who needs a prescription drug in liquid form yet no drug company makes the drug in this formulation)’. Usefully it also states that it ‘does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product’s manufacturer and other manufacturer directions consistent with that labeling’.

Extemporaneous dispensing/preparation

Label/labelling

The authorisation to market a product in the USA is contained in the ‘label’ (or labelling) approved by the FDA.

Manipulation

- for accurate administration of a smaller dose
  modification of a dosage form (e.g. splitting a tablet or transdermal patch) in an attempt to deliver an accurate, smaller dose to a child

- for convenient administration
  modification of a dosage form (e.g. crushing a tablet; opening a capsule and adding contents to food or liquid) to make it easier or more convenient to administer to a child

Manufacture

Marketing Authorisation

The authorisation to market a product in Europe is contained in the Marketing Authorisation approved by the EMA.

‘Off-label’

Use of a drug for purposes or routes or methods of administration other than approved in the label (USA) or Marketing Authorisation (EU).

‘Specials’

A drug product in UK which does not have a Marketing Authorisation but has been produced to the quality standards of GMP by a manufacturing unit licensed for such production. Whilst there may be assurances of quality, safety, efficacy and bioavailability have often not been studied.
Unlicensed

A drug that does not have an authorisation from the regulatory authority of the country in which it is being used. The drug may be authorised in another country or may have been prepared extemporaneously.

Potential guidance

3. Importation – cost, politics, counterfeits

3.1 If an appropriate medicine can be sourced, care should be taken to ensure that the medicine has been licensed for use and marketed in the country of origin, rather than being manufactured solely for export since quality standards may be different. (15)

3.2 The company used for importation should have adequate quality systems to ensure reputable sources, avoid counterfeits, maintain storage conditions and have a recall system for defective products (15). [provide a list of importers?]

3.3 Product information (for professionals and carers) may not be in an appropriate language. Some importers will provide translations but the pharmacist should be prepared to provide alternative information.

3.4 Regulatory barriers to importation in different countries will need to be addressed.