PROVISION BY HEALTH-CARE PROFESSIONALS OF PATIENT-SPECIFIC PREPARATIONS FOR CHILDREN THAT ARE NOT AVAILABLE AS AUTHORIZED PRODUCTS - POINTS TO CONSIDER¹

(This draft document was received from Dr S. Hill, Medicines Access and Rational Use and Secretary, WHO Expert Committee on the Selection and Use of Essential Medicines)

REVISED DRAFT FOR COMMENT

Should you have any comments on the attached revision, please send these to Dr S. Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, (kopp@who.int) with a copy to Ms Marie Gaspard (gaspardm@who.int) by 29 September 2011. Dr Kopp will coordinate with the secretariat of the above-mentioned Expert Committee.

Our working documents will be sent out electronically only and will also be placed on the Medicines web site for comment. If you do not already receive our draft specifications please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.

¹ The previous title of this document was Extemporaneous dispensing and administration of medicines to children - guidelines.
<table>
<thead>
<tr>
<th>Activity</th>
<th>Date</th>
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<tr>
<td>First draft prepared by Dr T. Nunn, UK, commissioned by Dr S. Hill, Medicines Access and Rational Use, Department of Essential Medicines and Pharmaceutical Policies, World Health Organization</td>
<td>March 2011</td>
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<tr>
<td>Discussion at informal consultation on paediatrics and generics guidelines development</td>
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<td>Revision prepared incorporating amendments by WHO committee</td>
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<td>10-14 October 2011</td>
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INTRODUCTION

*WHO Expert Committee on the Selection and Use for Essential Medicines*

The last meeting of the World Health Organization (WHO) Expert Committee on the Selection and Use for Essential Medicines took place in Accra, Ghana on 21-25 March 2011. Updates to the 17th WHO Model List of Essential Medicines and to the 3rd Model List of Essential Medicines for Children based on the recommendations of the Expert Committee can be found in the related report, currently available in its unedited version on the web.

The Committee also reviewed the current development of guidance on the extemporaneous preparation of medicines for children and noted the preliminary draft of guidance on extemporaneous preparation of medicines for children, commissioned by WHO.

The Committee accepted that there may be situations where extemporaneous preparation of medicines for children is necessary, but was concerned about the risks of inappropriate preparations. The Committee also considered the risks of diverting efforts aimed at the development of age-appropriate dosage forms for children and indicated that WHO endorsement of extemporaneous use should not be seen, in any way, as indicating a lack of
need for commercially available paediatric dosage forms. The Committee raised concerns about potentially conflicting signals arising from a WHO publication that might appear to endorse wider use of manipulation of adult dosage forms for children.


Notwithstanding these concerns, the Committee agreed that the document should be finalized for publication as a time-limited guidance that addresses the current need for advice, including review by the Expert Committee on the Specification of Pharmaceutical Preparations. Consideration may be given to publication of this guidance document by an organization other than WHO.

Informal Consultation on Paediatric and Generics guidelines, held in preparation of the WHO Expert Committee on the Specification of Pharmaceutical Preparations

The above conclusions were presented by the Secretary of the WHO Expert Committee on the Selection and Use for Essential Medicines and discussed during the informal consultation on Paediatric and Generics guidelines, held on 4-6 May 2011 under the auspices of the WHO Expert Committee on the Specification of Pharmaceutical Preparations. The participants suggested to modify the title to avoid reference to "extemporaneous", and be – although longer – of explanatory nature, in addition it was suggested to align the title of this document with other similar guidance texts currently under development as "points to consider".

Furthermore, the experts endorsed the recommendation of the WHO Expert Committee on the Selection and Use for Essential Medicines to prepare a time-limited version and in order to proceed towards such a publication, to send out widely this working document for comments and report the outcome to the forthcoming meeting of the Expert Committee on the Specification of Pharmaceutical Preparations.

1. SCENE OF DOCUMENT

Note
These points to consider are supported by a literature review of the evidence available. In reading this document, reference should be made to the relevant sections of the review for further information; ref. QAS/11.400.

1.1 Background

Children should have access to authorized, ready-to-use, age-appropriate preparations of medicines. Nothing in this document should detract from this objective. However, it is recognized that such preparations will not always be available and a safe and effective alternative must be sought.

In the context of neonatal and paediatric pharmacy practice compounding is the technique used by pharmacists to produce medicines from ingredients when no commercially available, authorized, age-appropriate dosage form exists. Compared to use of authorized 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 compounding of a medicine for a child may be the only option when there is no appropriate dosage form available. However, there may be other, safer and more
effective ways of delivering the required dose and the risks associated with compounding can be reduced when used as a last resort.

1.2 Purpose

The purpose of this advice is to:

1.2.1 To provide evidence-based or best practice advice and education about alternatives to compounding of medicines for children.

1.2.2 To describe and educate practitioners regarding the potential problems of compounding and how to avoid them.

1.2.3 To provide brief advice on compounding, if this is necessary as a last resort.

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

Wherever possible the advice is informed by the relevant evidence. However, the evidence base is weak or non-existent in most situations. Consequently, the advice is predominantly informed by best practice, based on sound scientific and therapeutic principles and expert consensus. Whilst this points-to-consider document is a working, practical document, it is important to invite comment and input from interested parties so that the advice can be developed further in response to feedback.

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

1.3 Target audience and health-care settings

This advice is intended for a wide audience of health-care stakeholders 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 organizations and national pharmacy associations;
- general hospitals and health clinics;
- Specialized paediatric hospitals and primary care clinics; and
- the pharmaceutical industry.

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 compounding preparations.
2. ALTERNATIVES TO COMPOUNDING

The risks and benefits of different approaches to providing preparations for administration to children should be assessed on a case-by-case basis.

The compounding 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.

For example, if the stability and method of preparation of a compounded 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, for example, the drug forms a caking suspension in the only available excipient (e.g. 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 work 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. A secure supply chain should be established according to local regulatory requirements. 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 compounded 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.

B. "Dose rounding"

If the dose prescribed does not correspond to a dosage form which is commercially available, consider whether the dose can be suitably 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. Available from: [http://apps.who.int/medicines/en/m/abstract/Js17151e/](http://apps.who.int/medicines/en/m/abstract/Js17151e/)

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.

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2 This includes products prepared to GMP standards, for example, in an accredited hospital manufacturing unit or "specials" laboratory.
Examples are presented in Appendix 1.

D. Dosage form alternatives

Consider strategies to increase assurance that a more effective and safer product can be delivered. There are a number of alternatives to compounding an oral liquid especially if the stability of an oral liquid cannot be assured. These include:

(i) tablet splitting
Tables 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 (age will vary but usually from age 6–8 years 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.

Not all tablets should be split. In general, those with a sustained release or enteric coating should not be split but it may be possible to split those with a sustained release matrix. Formularies or manufacturer’s information should be consulted.

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

(ii) tablet/capsule dispersion
It may be possible to disperse tablets or the contents of capsules 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. Volume of fluid and extraction time should be considered.

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.
Potential for storage and reuse of the dispersion should be considered. In general such dispersions should be used at once unless microbiological and other stability aspects have been satisfactorily investigated and safe storage can be assured.

The World Health Organization (WHO) is promoting the use of flexible solid oral dosage forms such as dispersible tablets. 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 common 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. SmPC/label information for 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.

Aliquots should not usually be taken from liquid-filled capsules since it is difficult to remove and measure the total contents;

(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, e.g. first-pass effect; gastric acidity. Some injections (e.g. proteins, insulin) should not be given orally.

It may be an expensive option. It is recommended that specialist advice, e.g. consultation with a medicines information centre, is sought before this alternative is considered.

Some examples are described in Appendix 2;

(v) splitting suppositories
There is little information on the accuracy with which suppositories can be split and uniformity of drug content in the dosage form may present problems. Suppositories have been melted and recast into smaller moulds. Therapeutic index and the consequences of over- or under-dosing should be taken into account when determining whether it is safe to split suppositories. If possible, this should be done in the pharmacy and segments weighed.

Suppositories should not be given orally;

(vi) other possibilities
It may also be possible to give oral liquids and injections by the rectal route. Some injections may also be administered bucally and intranasally. Advice should be sought from formularies and the literature.
3. COMPOUNDING

3.1 Potential problems and how to avoid them

Compounding 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 7 of the review; ref. QAS/11.400.

3.2 Basic considerations for extemporaneous formulations

- **Prefer using an authorized dosage form as the starting point**
  It may be safer and more effective to crush tablets or use the contents of solid-filled capsules with an appropriate suspending vehicle rather than preparing from active chemical ingredients and excipients. There are many formulations available with validated shelf-life but sourcing of suspending agents may be difficult and/or expensive. If using an active pharmaceutical ingredient (API) and excipients, ensure the quality of the ingredients.

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

- **Apply the principles of GMP**
  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 dispensing 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:
  - avoid cross-contamination;
  - avoid microbial contamination;
  - assure authenticity of ingredients;
  - protect the operator; and
  - keep proper records.

  Further guidance is given in Appendix 3.

- **Dose uniformity may be a problem – explain importance of resuspension**
  If the drug is insoluble it will generally be more chemically stable in a liquid formulation but uniformity of dosing may be a problem. Because a suspending agent will be required, check that the finished preparation resuspends under in-use conditions and explain the importance of resuspension to patients/carers.
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 compounded liquid preparations should be shaken immediately 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, bioavailability and stability. Consult specialist advice if possible.

Similarly, the results of a published study using a drug mixed with a commercial suspending base 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 information on the formulation of a preparation is available**
The pharmacist must assess the risks for different options and use knowledge and experience to formulate a product.

  - **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 API at the expected concentration in the final product. The Merck Index may be useful.

  - **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 resuspension and pouring, degree of caking on storage, observation of physical behaviour and characteristics.
Consider risk of microbial growth
All compounded liquid 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 rapid growth of bacteria and fungi especially at warm to hot temperatures and can pose hazards to patients especially if immunosuppressed.

Preparation of compounded liquids should be carried out under conditions to minimize 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 are being reused should be thoroughly washed, rinsed with sterile or freshly boiled water and dried. Light-protective (e.g. dark plastic or amber glass) containers should generally be used. Consider the use of a light-protective wrapping such as foil if a light-protective container is not available.

- Label information
  Include at least the following information (in addition to dosage directions):
  - name of drug and preparation;
  - storage requirements;
  - "Shake the bottle" – if appropriate;
  - do not use after (expiry date);
  - reference or batch number (or date of preparation);
  - pharmacy name and contact information;
  - name of patient and date of dispensing; and
  - any special precautions or warnings.

- 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 two weeks (or less if advised in the published study or if antimicrobial preservatives cannot be used) is applied to all compounded preparations. This will
encourage regular fresh preparations 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 care givers/patients**
  This may include instructions on storage, resuspension, 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 dialogue with regulatory bodies and international agencies and networks about problems and concerns associated with the preparation and availability of age appropriate medicines for children. The sharing of solutions to problems is also important.

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 formulations and medicines administration to children have been published. Consulting these documents may assist in forming local policies of practice and educational activities for practitioners.

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.

4.3 **Source and supply**

A database of sources and prices of medicines for children has been compiled by the United Nations Children's Fund (UNICEF). 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 database can be searched to find worldwide suppliers of oral liquids and other age-appropriate formulations for paediatric use.
4.4 Networks and information services

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

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

4.4.3 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/.

5. GUIDANCE FOR HEALTH AUTHORITIES, REGULATORS AND SUPPLIERS

5.1 Health authorities and regulators should work with practitioners (pharmacists, physicians and paediatricians) to source and make age-appropriate formulations available.

5.2 If possible, therapeutic and dosage form alternatives (including dispersible tablets) to compounded preparations should be sourced and publicized where sufficient evidence is available to support the practice.

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 to age-appropriate formulations.

5.4 Manufacturers are encouraged to include industry-validated dosage form manipulations and compounded formulations in their product literature if possible or to make such information available on request.

6. GUIDANCE FOR RESEARCHERS

6.1 Ongoing research on compounded formulations and the manipulation of dosage forms is important.

6.2 Most compounded formulation 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.

6.3 Most of the information about manipulation of dosage forms concerns splitting of tablets. Researchers are encouraged to investigate other manipulations to ensure that they can be undertaken safely and accurately and that the anticipated dose is delivered and bioavailable.
7. PRACTICAL SCENARIOS

Some practice scenarios are outlined in Appendix 8 of the review document (ref. QAS/11.400) to explain some of the principles described above.

8. REFERENCES


5. WHO good manufacturing practices
   - Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, CD-ROM 2010;
6. The International Pharmacopoeia (Ph. Int.)
   • The International Pharmacopoeia, Fourth Edition (including First and Second Supplements), online and CD-ROM version 2011
ANNEX 1

EXAMPLES OF THERAPEUTIC ALTERNATIVES TO COMPOUNDED PREPARATIONS

<table>
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<tr>
<th>Required</th>
<th>Possible alternative</th>
<th>Notes</th>
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<td>Enalapril liquid</td>
<td>Captopril liquid</td>
<td>Available commercially in some countries.</td>
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<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. 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>
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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).
ANNEX 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 is possible that the drug will be absorbed enterally 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 oral 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, e.g. propylene glycol and ethanol. The pH of some injection solutions may mean that they should not be given orally or be diluted before administration to avoid local irritation, e.g. furosemide injection (pH 9), pantoprazole injection (pH 9-10.5), phenytoin sodium injection (pH 10-12).

Injections will usually require taste masking by addition to a suitable liquid or food immediately before administration.

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.
ANNEX 3

GUIDE TO GMP FOR EXTEMPORANEOUS FORMULATIONS

This guideline does not include details of GMP which is a philosophy of practice and process to assure the quality and safety of prepared pharmaceuticals. Whilst developed for large-scale manufacture, these principles are just as important with small-scale extemporaneous preparations but most hospitals and dispensaries do not have sufficient facilities and resources to fully comply.

The following documents should be referred to so that a best practice process can be developed to govern the quality and safety of extemporaneously prepared medicines.

Guidelines or standard operating procedures produced locally for extemporaneous preparation or small-scale manufacture should take these principles into account.

**Useful resources include:**

**Pharmaceutical Inspection Co-operation Scheme**

http://www.picscheme.org/

In particular the following documents which can be downloaded free of charge:

PE 009-9 (Part I)

PIC/S GMP GUIDE (PART I: BASIC REQUIREMENTS FOR MEDICINAL PRODUCTS)

PE 010-3

GUIDE TO GOOD PRACTICES FOR THE PREPARATION OF MEDICINAL PRODUCTS IN HEALTHCARE ESTABLISHMENTS (PE 010-3).

**Handbook of Extemporaneous Preparation: A guide to pharmaceutical compounding**


As a result of these guidelines and the feedback received more specific guidelines and minimum standards for extemporaneous preparation will be developed. These will be explained in future training programmes.

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