FIP-WHO TECHNICAL GUIDELINES:
CONSIDERATIONS ON THE PROVISION BY HEALTH-CARE PROFESSIONALS OF PATIENT-SPECIFIC ENTERAL COMPOUNDING FOR SPECIAL POPULATIONS (FOR EXAMPLE, PAEDIATRIC AND GERIATRIC PATIENTS) WHEN NO SUITABLE AUTHORIZED PRODUCTS ARE AVAILABLE

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 30 September 2012. 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.

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Please send any request for permission to:

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1 The previous title of this document was Extemporaneous dispensing and administration of medicines to children – guidelines.
SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/12.509: FIP-WHO TECHNICAL GUIDELINES: CONSIDERATIONS ON THE PROVISION BY HEALTH-CARE PROFESSIONALS OF PATIENT-SPECIFIC ENTERAL COMPOUNDING FOR SPECIAL POPULATIONS (FOR EXAMPLE, PAEDIATRIC AND GERIATRIC PATIENTS) WHEN NO SUITABLE AUTHORIZED PRODUCTS ARE AVAILABLE

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Note from the secretariat:

The first draft of this document (working document QAS/11.399: Extemporaneous dispensing and administration of medicines to children – guidelines) was received from the Medicines Access and Rational Use Team, WHO Department of Essential Medicines and Health Products, and Secretary, WHO Expert Committee on the Selection and Use of Essential Medicines. It has been newly expanded to cover special populations (e.g. paediatric and geriatric patents) and is intended as joint FIP-WHO technical guidelines.

The document is 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: Report for WHO on findings of a review of existing guidance/advisory documents on how medicines should be administered to children, including general instructions on extemporaneous preparations and manipulation of adult dosage forms.
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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. **SCOPE OF DOCUMENT**

1.1 **Background**

Special populations in the context of this document are defined as children or adults with swallowing difficulties or tube feeds as a consequence of ageing or a medical condition. Children should have access to authorized, age-appropriate preparations of medicines. Adults with swallowing difficulties or tube feeds should have access to formulations that facilitate the safe and effective administration of medication. 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 some situations compounding of a medicine may be the only option when there is no appropriate dosage form available. One must always strive to deliver medication in the safest and most effective way possible, with compounding left as a last resort once the risks are minimized.

In the context of pharmacy practice, compounding is the technique used by pharmacists to produce medicines from ingredients when no commercially available, authorized, age-appropriate or adequate dosage form exists. Compared to the use of authorized medicines there are potential significant risks; quality, safety and efficacy can rarely all be assured. There have been many errors reported in the preparation of such medicines. Compounding does not apply to reconstitution of authorized medicine prior to dispensing.

1.2 **Purpose**

The purpose of this document is:

1.2.1 To provide evidence-based or best practice advice about alternatives to compounding of medicines for special populations.

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 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. While 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, references are 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 pharmacist associations;
- general hospitals and health clinics;
- Specialized paediatric hospitals and primary care clinics

Extemporaneous compounding may be particularly useful in many clinical situations. For example, patients with swallowing difficulties require age-appropriate tube feeds. In these cases it may be difficult to obtain relevant information and/or achieve the highest standards of quality assurance when compounding preparations.

2. ALTERNATIVES TO COMPOUNDING

Before compounding medicines, pharmacists should take into account the following considerations. Please refer to the chapter mentioned for more information.

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

The compounding of a liquid medicine from a solid dosage form (tablet or capsule) should generally be considered as a last resort. Before deciding to compound, consider therapeutic alternatives, sourcing commercially available formulations, using industry verified and approved compounding, dose rounding, tablet splitting, tablet or capsule dispersion, or crushing and using injectable formulations orally.

2.1 Oral administration

A. Sourcing of a commercially available or manufactured\(^2\) 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.

Authorized importation of products may be expensive and reputable suppliers should be used to avoid spurious/falsely-labelled/falsified/counterfeit medicines. 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 is provided in the local language.

\(^2\) This includes products prepared to GMP standards, for example, in an accredited hospital manufacturing unit or "specials" laboratory.
B. Therapeutic alternatives

If a medicine is required in a formulation which is not available (e.g. in an age-appropriate form) consider the possibility of using a medicine with a similar therapeutic action but which is available in a more suitable form.

Examples are presented in Annex 1.
C. "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. Width of the drug’s therapeutic index and patient characteristics are to be considered before making a decision.

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 range. Consult the WHO Model Formulary for Children. Available from: http://apps.who.int/medicinedocs/en/m/abstract/Js17151e/

D. Dosage form alternatives

In situations where the dose is less than what is commercially available or there are swallowing difficulties, consider the following:

(i) Tablet splitting

Not all tablets can be split to meet pharmacopoeia requirements for uniformity of mass of subdivided parts. Thus, evaluate on a case-by-case basis whether splitting tablets might lead to toxicity or reduced effect.

Tablets may 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.

Moreover, tablet splitting is not always advisable given the characteristics of the formulation. In general, those with sustained-release or enteric coatings should not be split unless supported by the manufacturer.

Consideration should be given to splitting tablets with an appropriate commercial tablet splitter in the pharmacy. If possible, tablets with score lines 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 immediate-release 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 as required. If the tablet disperses readily, dispersing the tablet in a known volume of water can allow a fractional dose to be accurately measured with a syringe. As extraction of soluble drug from the tablet excipients may be incomplete, the suspension should be shaken or stirred prior to measuring the dose. The dispersed medicine should not be filtered unless it has been established that active drug is not removed. Volume of fluid and extraction time should be considered. If the dose is not administered immediately or if there is no stability data, the remainder should be discarded. Not all tablets disperse readily but some form suspensions in seconds.
In the case of an insoluble tablet or capsule, the full dose can be administered by regular rinsing of the containers to moisten trace remnants. The measurement of a fractional dose by taking an aliquot from a suspension formed in this way can be done only if there is not rapid sedimentation. If rapid sedimentation occurs, dose fractioning should not be done as it will result in dosage inaccuracy. Tablet dispersion may not always be practical for infants if the tablet is not scored or when the doses required equal small tablet fractions that are unable to be reliably prepared, e.g. a fifth of a tablet.

Storage and reuse of the dispersion should not be considered. In general, such dispersions should be used at once unless microbiological and other stability aspects have been satisfactorily investigated and storage according to pharmacopoeial standards can be assured.

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 are trained appropriately on how they are to be administered;

(iii) Crushing tablets/opening capsules and mixing powder with food or a drink

The practice of crushing immediate release tablets or opening capsules and adding the contents to a palatable drink or sprinkling onto solid food are common alternatives. There may be little evidence to support the efficacy of this method (since stability and bioavailability may be altered). If this process is chosen, then information should be sought from manufacturers (e.g. Summary of Product Characteristics (SmPC)/label information for oseltamivir) and it is an acceptable practice only if the bioavailability is not affected by food and the product is used immediately. It is also difficult to ensure that a complete dose has been taken. Handling powdered drugs may present health concerns for nurses and carers. Tablet dispersion may be a simpler, more reliable and potentially safer method. Practitioners must never mix drugs with formula or breast milk, as it could cause the infant to refuse their only source of nutrition.

Aliquots should not usually be taken from liquid-filled capsules since it is difficult to remove and measure the total contents. In addition, a list of commercial dosage forms that cannot be crushed or altered is seen in Annex 2. Such a list is not exhaustive.

(iv) Preparing powder sachets from crushed tablets

There will be instances where patient-specific medications are not scored for dosing or a suitable dose cannot be achieved through multiple scored tablets. If the medication of choice can be crushed, the pharmacist should select the correct number of tablets as per dosing guidelines, crush them, and package a portion of powder in a ready-to-use single dose aliquot. This method avoids stability or solubility issues and allows for dispensing of single doses to be reconstituted in a liquid vehicle and consumed by the patient.

(v) Giving the injectable form by the oral route

This technique is appropriate for some medications, but there are important factors which must first be considered, e.g. first-pass effect, gastric acidity. Some injections (e.g. proteins, insulin) should not be given orally.
This may be an expensive option. It is recommended that specialized advice, e.g. consultation with a medicine information centre, is sought before this alternative is considered.

Some examples are described in Annex 3.

2.2 Rectal administration

A. Splitting suppositories

There is little information on the accuracy with which suppositories can be split and uniformity of drug content throughout the dosage form may present problems. Melting suppositories recast into smaller moulds should be discouraged as the distribution of the active ingredient can be affected and result in over- or under-dosing. Therapeutic indices 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 upon weighing of segments.

Suppositories should not be given orally.

B. Other possibilities

It may be possible to give oral liquids and injections by the rectal route. Annex 4 discusses this fact and provides literature references. Some injections may also be administered orally and intranasally. Advice should be sought from formularies and the literature. In addition, one must evaluate contraindications that may be specific to the patient. For example, one would not administer a medication rectally to an immunosuppressed patient, for fear of rectal bleeding and infection.

Only when no other solutions are possible, should compounding be considered.

3. COMPOUNDING

The large-scale use of compounded oral liquids for special populations should not be justified on the grounds that they are cheaper than commercial products. Other options, including local manufacturing using good manufacturing practices (GMP) standards, should be investigated.

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 issues that may arise 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

Compounding with an active pharmaceutical ingredient (API) will increase the likelihood of medication errors during the compounding process through improper dosing calculations, use of improper ingredient grades, introduction of foreign impurities, introduction of incompatible excipients, mixing errors, etc. If using an API and excipients, ensure the quality
of the ingredients meets pharmacopoeia standards. If no stability or purity information can be obtained, the practitioner should not compound extemporaneously or alter the ingredients directly prior to patient administration.

Established preparations can be found from international hospital resources.

- ** Prefer using an authorized dosage form as the starting point**
  It is safer and more effective to crush tablets or use the contents of solid-filled capsules with an appropriate suspending vehicle rather than preparing products from active chemical ingredients or excipients. There are many formulations available with validated stabilities 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 product information and the latest national and international guidelines and/or specialist information centres if possible.

- ** Apply the principles of GMP and/or good compounding practices**
  These involve 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;
  - keep proper records.

  A double-check of all calculations including a second practitioner’s signature is a common best practice.

  Further guidance is given in Annex 5.

  **Dose uniformity may be a problem – 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.

- **Commercially available preparations will require suspending agents during the conversion to a liquid preparation**
All compounded liquid preparations should be shaken immediately prior to administration as drug particles may not be in solution, even if considered highly soluble.

- **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. If possible, consult the pharmacopoeias as stated previously.

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 profiles 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. This information can be obtained through formularies or national pharmacopoeias.
  
  - **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. As an alternative, adding simple syrup beyond 65% w/w prevents microbial growth. Oral liquids that are not adequately preserved will
support rapid growth of bacteria and fungi especially at warm to hot
temperatures and can pose hazards to patients especially if immunosuppressed.

Preparation of compounded liquids should be carried out under conditions to
minimize the introduction of microbial contamination (see Annex 5).

- **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. Child-proof containers are recommended for safety.

- **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;
  - any special precautions or warnings.

- **Consider in-use storage**
  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 include 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**
  Chemical stability and potential for microbial growth under patient-use conditions are seldom tested in published studies. It is recommended that each compounded preparation be given an expiry date according to published storage and temperature conditions. 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 instructions to care-givers/patients**
  These may include instructions on storage, resuspension, changes in taste, smell or appearance and adverse effects. Ensuring palatability and masking taste is essential for special populations. For example, one can add powdered dosage forms to water, juice or sweet substances such as jam, apple sauce, chocolate pudding and crushed bananas. Children can consume cold substances prior or after taking medication and attempt to conceal the flavour with strong cheese or chewing gum. Liquids can also be given to the sides of the mouth to avoid taste buds. 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 medicine administration to special populations 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) is being developed to provide comprehensive information for all settings and environments.

4.3 **Source and supply**

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 medicine 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 eMxt 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.  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.

Note from the secretariat: References will be sorted in the final version.

6.  REFERENCES


5.  WHO good manufacturing practices

- Quality assurance of pharmaceuticals; a compendium of guidelines and related materials, CD-ROM 2010;
WHO good manufacturing practices: main principles for pharmaceutical products
Active pharmaceutical ingredients (bulk drug substances)
Pharmaceutical excipients
WHO good manufacturing practices for sterile pharmaceutical products
Pharmaceutical products containing hazardous substances [pdf 1Mb]
Investigational pharmaceutical products for clinical trials in humans [pdf 4Mb]
Herbal medicinal products [pdf 4Mb]
Radiopharmaceutical products [pdf 632kb]
Water for pharmaceutical use
WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms
Validation

Risk analysis
Application of Hazard Analysis and Critical Control Point (HACCP) Methodology in Pharmaceuticals [pdf 632kb]

Technology transfer
WHO guidelines on transfer of technology in pharmaceutical manufacturing

Reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations:

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**

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</tbody>
</table>

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).
There are several reasons why an oral dosage form should not be crushed. For example, this process might alter a specific coating that is required for controlled delivery of the active ingredient. In turn, this would change absorption patterns in patients. Similarly, there may be a desired duration of action associated with the oral dosage form that is altered when the drug is crushed. In addition, there is the possibility of gastric irritation to the patient upon ingestion of a crushed product.

With these in mind, the Institute for Safe Medication Practices has prepared a list of dosage forms that should not be crushed. Each medication is accompanied by an explanation. This list is not exhaustive; however, it provides an informative guide for many common drug products.

ANNEX 3

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 active 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.

Oral use of the injectable form of a drug which is subject 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 for an oral dose of 15 mg.

Drugs such as enalaprilat which are administered orally as pro-drugs (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 suggest 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 4

EXAMPLES OF ALTERNATE DOSAGE FORMS ADMINISTERED RECTALLY

Non-rectal dosage forms can be obtained for treatment of an individual patient and its rectal use should be limited to the following list of approved products (1-3).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Product to be given rectally (no substitution)</th>
<th>Doses for rectal liquid administration</th>
<th>Rectal bio-availability</th>
<th>Dilution</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Suspension (80 mg/mL)</td>
<td>&lt;120 mg</td>
<td>30-40% (oral bioavail: 60 – 98%)</td>
<td>None</td>
<td>120mg, 325mg and 650mg suppositories available.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Suspension (20 mg/mL) or tablet (100 mg or 200 mg)</td>
<td>n/a</td>
<td>&gt;90%</td>
<td>Dilute 1:1 with water</td>
<td>-Not for status epilepticus -Suspension provokes strong urge to defaecate; use crushed tablets if possible</td>
</tr>
<tr>
<td>Chloral Hydrate</td>
<td>Syrup (100 mg/mL)</td>
<td>&lt;500 mg</td>
<td>100%</td>
<td>None</td>
<td>-Use IV formulation -Rectal burning sensation caused by propylene glycol reported in 60%</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Injection (5mg/mL)</td>
<td>Max 10 mg</td>
<td>100%</td>
<td>None</td>
<td>-Use IV formulation -Rectal burning sensation caused by propylene glycol reported in 60%</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Injection (50mg/mL)</td>
<td>&lt;25mg</td>
<td>n/a</td>
<td>None</td>
<td>25mg, 50mg and 100 mg suppositories available.</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Injection (4mg/mL)</td>
<td>n/a</td>
<td>&gt;80%</td>
<td>Dilute 1:1 with water</td>
<td>-Use IV formulation -Not for status epilepticus -serum concentration less than half than IV route</td>
</tr>
<tr>
<td>Morphine Sulphate</td>
<td>syrup (1mg/mL)</td>
<td>&lt;5mg</td>
<td>27% (oral bioavail: 30 - 40%)</td>
<td>None</td>
<td>5mg, 10mg and 30mg suppositories are available.</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Solution (0.8 mg/mL)</td>
<td></td>
<td>58%</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Paraldehyde</td>
<td>Injection (100%)</td>
<td>Max 5 mL</td>
<td>83%</td>
<td>Dilute 1:1 with mineral oil</td>
<td>-Use glass syringe</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Injection (60 mg/mL)</td>
<td>n/a</td>
<td>90-100%</td>
<td>none</td>
<td>-Use IV formulation -Special Access Programme drug</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Syrup (50mg/mL)</td>
<td>n/a</td>
<td>85%</td>
<td>none</td>
<td>-administer as 3 divided doses</td>
</tr>
</tbody>
</table>
Procedure:

Procedure for administration of liquids rectally

6.1 Draw up solution with the smallest syringe that accommodates the dose, no larger than 1mL for an infant, 3mL for an older child.

6.2 Draw into the syringe an equal amount of diluent (if necessary) and mix contents thoroughly by gently inverting syringe.

6.3 Lubricate syringe with sterile water-soluble lubricant. Avoid placement of syringe or catheter into faecal mass.

6.4 In most cases administer by placing barrel of syringe directly into the rectum (1.5 inches, at most 5 centimeters). This is similar to taking a rectal temperature with an inserted thermometer.

6.5 Inject the contents slowly while squeezing buttocks together. Remove syringe and continue to squeeze buttocks for a few minutes.

6.6 If the syringe is too large for insertion into the rectum attach a red rubber catheter or feeding tube to the end of the syringe. You may have to cut the top of the catheter or feeding tube to create a good fit around the tip of the syringe so fluid or medication does not leak out. Flush with drug solution to remove air and note the volume required to prime the tubing. Insert into rectum well beyond the anal sphincter before injecting slowly. Flush with air or water in the same volume as for priming.

References


ANNEX 5

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 manufacturers, these principles are just as important in 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 ensure 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:

Volume 2, 2nd updated edition

WHO good manufacturing practices: main principles for pharmaceutical products

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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