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 compounding preparations and manipulation of adult dosage forms

(This draft document was prepared by Dr T. Nunn, United Kingdom for
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and Secretary, WHO Expert Committee on the
Selection and Use of Essential Medicines)

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**SCHEDULE OF DOCUMENT 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 compounded preparations and manipulation of adult dosage forms

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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 compounded preparations and manipulation of adult dosage forms

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1. INTRODUCTION

1.1 Medicines for children should be studied and appropriately authorized for quality, safety and efficacy and should be formulated in dosage forms acceptable to the age of the child to be treated (1). Whilst many such dosage forms for oral use should be pleasant-tasting liquids there is advice that in resource-poor countries, flexible solid oral dosage forms may be cheaper to produce, store and transport (2).
1.2 Many of the medicines required for children are not available in authorized, age-appropriate formulations \((3,4)\). 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 \((5)\). When medicines are used "off-label" for children, dosage forms may have been designed only for adults. In some circumstances no appropriate medicine is available and preparations are made from chemical ingredients (e.g. for some inborn errors of metabolism).

1.3 Those medicines that are appropriate for children may not be available in the countries that require them \((6, 7)\).

1.4 The problem of poor access to medicines for children may be overcome in several ways including importation of age-appropriate formulations, compounding (or extemporaneous dispensing/preparation) from other authorized dosage forms or from active drugs and excipients and manipulation of other dosage forms in an attempt to provide an accurate paediatric dose \((8)\). The term "compounding" has been preferred in this paper (see glossary).

1.5 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 for pneumonia, oral omeprazole) or therapeutic substitution of a similar drug for which a more appropriate dosage form is available \((9)\).

1.6 The alternatives to using an authorized, age-appropriate dosage form are all associated with different degrees of risk to the patient. Compounding, with little if any quality assurance, carries significant risk of error, unknown efficacy and toxicity and there are many reports of significant harm \((10, 11)\).

1.7 Compounding is poorly defined and may also be known as "extemporaneous preparation or dispensing". A working definition used by Brion F et al \((12)\) 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 "extemporaneous", "magistral" and "officianale" preparation may also be used (see Glossary).

1.8 This paper reviews the literature providing standards and guidelines for compounding\(^1\) and manipulation of dosage forms attempting to provide accurate paediatric doses and considers guidance on strategies to avoid compounding. The search strategy is outlined in Annex 1. Methodology. Statements are referenced but a bibliography by topic is also provided as Annex 4. Selected Bibliography. Where secondary guidelines are not available some of the primary literature has been reviewed and summarized. The paper will inform (and should be used with) guidelines and recommendations to the WHO Expert Committee on the Essential Medicines List.

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\(^1\) This paper does not set out to consider manufacturing of medicines to good manufacturing practice (GMP) 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.
### 2. ACCESS TO AGE-APPROPRIATE FORMULATIONS

2.1 Many paediatric age-appropriate medicines (e.g. oral liquids) are authorized 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 health-care 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: [www.medicinesforchildren.org.uk](http://www.medicinesforchildren.org.uk)).

2.3 However, manufacturers may not make their medicines available in all countries even within a defined region (12).

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.

2.4.1 **UNICEF information on sources and prices**
UNICEF publishes information on the availability and cost of many medicines including medicines for children (13) and will soon make the information available as a database called "CHILDmed". 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.

2.4.2 **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.

2.4.3 In the United Kingdom the medicines regulator (MHRA) has recently changed the way in which appropriately authorized wholesaler dealers and manufacturers can make health-care professionals aware of the imported and other unlicensed medicines they have available (14). This includes the availability of medicines licensed in other countries and may make dissemination of such information easier.

### Conclusion

Age-appropriate dosage forms may be authorized and available but frequently they are not available in all countries that require them and it may not be economically feasible to source them.

### Recommendation

Steps should be taken to ensure that all medicines on the paediatric priority list are available at affordable prices in all countries. Information should be provided on the availability and price of all age-appropriate dosage forms on the Essential Medicines List for Children.
3. OPTIONS WHEN AGE-APPROPRIATE DOSAGE FORMS ARE NOT AVAILABLE

Annex 8 provides some scenarios as practical examples of options that avoid compounding a medicine.

3.1 Therapeutic substitution (8, 9, 15)

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 a compounded 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).

Conclusion

It may be possible to substitute with another drug in the same or similar therapeutic class if the other drug has a more suitable dosage form. However, most information is about therapeutic substitution in adults so pharmacists may have to use their professional judgement to decide whether therapeutic substitution is suitable for an individual patient.

Recommendation

There should be a systematic review of drugs and dosage forms and guidance prepared on common therapeutic substitutions that might be investigated for children.

3.2 Rounding of doses

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 and appropriate (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 (when a large dose range of 0.7-3mg/kg/day often means the dose can be rounded to enable a dispersible MUPS® tablet to be used), fixed-dose combination antiretrovirals for HIV/AIDS, mefloquine.

Several treatment guidelines and formularies recognize 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 antiretrovirals for the treatment of HIV in infants and children (16).
Conclusion

It may be possible to "round" the calculated paediatric dose to the nearest convenient dosage form if therapeutic index allows. Information is available in published formularies but information on PK and PD relationships may not always be available. In these circumstances the pharmacist must use professional judgement to decide whether rounding of doses will be suitable for the individual patient.

Recommendation

WHO should ensure that the model formulary contains information on those drugs for which dose rounding may be appropriate.

3.3   Using an authorized medicine in an "off-label" manner

3.3.1 Authorized medicines used in ways other than those covered by the SmPC or label are said to be used "off-label" (see Glossary).

3.3.2 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 in an attempt to provide an accurate dose for a child.

3.3.3 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 British National Formulary for Children and WHO Model Formulary for Children to support use).

3.3.4 Medicines administered by different routes or manipulated (see Glossary) in an attempt 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 (see section 3.6).

3.3.5 Young children are often not capable of alerting health-care professionals or carers to any adverse drug effects they may be experiencing.

3.3.6 Manufacturers may not be prepared to provide relevant information when medicines are not used according to their authorization but their information departments should be consulted. 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 (see E-DRUG http://www.essentialdrugs.org/edrug/).

Recommendation

WHO should encourage manufacturers to investigate and provide information on all paediatric uses of medicines whether authorized or not.

WHO should encourage paediatric centres to establish links and share relevant information.
3.4 General guidance on alternative routes of administration

3.4.1 Use of a preparation intended for a different route

It may be possible to use an authorized dosage form via an alternative route of administration, e.g. use of an injection solution by the oral route or the use of oral liquids rectally. There are important factors that must be considered:

- Use of an injection solution orally

The following factors should be considered (1, 8, 17, 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 (8). 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 it will have very poor oral bioavailability;
- will the pH of the solution be tolerated? Extremes of pH could adversely affect the gastric mucosa (e.g. furosemide injection pH 9);
- 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; and
- cost may be prohibitive.

- Oral liquids administered rectally (18)

For children unable to take medicines by the oral route, it may be possible to administer oral liquids as an enema 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-ionized. In their guidance on rectal administration of anticonvulsants, Smith S et al (18) 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; and
- osmolarity: consider dilution of the solution/suspension if of high osmolarity to minimize the urge to defecate.
• Intravenous injections administered rectally

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 increased lipid solubility.

• Intravenous injections administered by other routes

Midazolam is commonly administered into the buccal cavity to control convulsions and intranasally as a sedative. Fentanyl and diamorphine injections have also been administered nasally (19).

Conclusion

Whilst only limited information is available, it may be possible to administer dosage forms by routes of administration not included in the authorization/label. Such administration should be supported by adequate references, preferably within a recognized paediatric formulary.

3.5 General guidance on manipulating dosage forms for accurate administration of doses to children

There are no guidelines on manipulation of dosage forms to achieve administration of accurate, smaller doses to children. In the UK, the MODRIC (20) research project is undertaking observational and questionnaire studies, a systematic review and risk assessment of manipulations in paediatric practice. An expert panel is developing a guideline on the manipulation of medicines to deliver accurate and reproducible doses to paediatric patients where no suitable age-appropriate product is available and publication is expected in the final quarter 2011.

Recommendation

WHO should consider the guidance produced by the MODRIC research group and make reference to it in WHO guidance if appropriate.

3.6 Guidance on specific manipulations

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 (1). 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 accuracy (even with the use of a tablet cutter which may not be readily available in some countries). This could have a significant effect on the patient, particularly for those drugs with a narrow therapeutic range when an insufficient dose could lead to treatment failure and a larger than expected dose could lead to toxicity.

Teng J (21) examined the division of 11 commonly split tablets and evaluated the resulting half-tablets for content uniformity using the USP Uniformity of Dosage Units test (22). 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 RB et al (23) considered the tablet splitting of levothyroxine, a drug with a narrow therapeutic range 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 (24) determined the level of weight uniformity of segments from tablets cut into halves and dispensed by pharmacists. Five-hundred and sixty 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 C et al (25) 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) a splitting device (Pilomat®), (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 the mechanism 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 (26).

The WHO guidance on dosing of antiretrovirals for children with HIV/AIDS is based on the ability to halve tablets (27).
Conclusion

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.

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®) 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.

Recommendation

WHO/UNICEF should consider which tablets are most frequently manipulated to achieve accurate, smaller doses for children and seek assurances from manufacturers.

3.6.2 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 (8, 28).

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 (29) 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 an isoniazid tablet crushed and mixed with apple sauce, parenteral isoniazid mixed with apple juice and 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 EK et al (30) 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 under-dosed because of the use of inadequate measuring devices by their parents. Standing J and Wong I (31) comment that there was no description of the accuracy of segmentation and 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; and
− exposure of 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 (9, 32, 33, 34, 35, 15).

As there are 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.

General references (36, 37, 38, 39, 40) discussing which solid oral dosage forms may be crushed to facilitate swallowing may also be of use when extrapolating practice to children. In general, enteric-coated, buccal, sublingual and most extended-release formulations should not be crushed.

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 (41). A therapeutic alternative such as amlodipine may be preferred.

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.

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

To aid administration, the capsule contents or crushed tablets described above may need to be dispersed in water, other liquid or soft food. All the potential risks associated with crushing tablets will obviously also apply 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 (15, 42). 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 the entire 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 (8, 15, 43, 44). 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 (45)) dispersed in water, generally these data are 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 (46). The preparation and administration of doses from dispersing tablets or capsules 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 probably preferable to segment the tablet and then disperse in liquid for administration.

The availability of oro-dispersible tablets or lyophilized 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 using breast milk to make this an option even in the very youngest babies.

**Recommendation**

Information should be generated on medicines that can or cannot be dispersed in liquid so that an accurate dose can be obtained by measuring a proportion. Such information should be included in the model formulary for children.

### 3.6.4 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 (47).

A study by Kim TW et al (48) examined 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 compounded. 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. COMPOUNDING

There will 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 compound a medicine.

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 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 (1, 49).

Conclusion

Use of powders is a common practice in some countries (e.g. European countries such as Finland and Italy (12) and Japan) but in general there is little information on any effects on bioavailability and or stability of the active ingredient.

4.1 Dangers

Compounding 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 a formulation (15).

4.2 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. Standardizing compounding practices and harmonizing 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 M et al (50) report on significant differences in the concept, definition, type and legal status of compounded products in Portugal and the UK. Compounding is a far more common practice in European countries such as Germany, Portugal and Spain than in the UK where community pharmacists primarily dispense "specials" instead of compounding medicines. In addition, German and Portuguese pharmacists have official formularies for compounded preparations so there is more standardization of prescriptions.

Brion F et al (12) 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 compounded medicines were available as suitable, authorized products in other countries. Information was requested on the most frequent compounded oral liquid, powder and capsule and on their formulation and stability. Twenty-one questionnaires from 16 countries were returned and showed the methods of preparation varied 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 compounded 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.

The Commonwealth Pharmacists Association (personal communication) surveyed Anglophone African countries in 2010. Eleven respondents described preparation of 60 different products of which 33 (55%) were available as licensed, age-appropriate formulations in the UK. The most commonly prepared were furosemide and quinine oral liquids.

Annex 7 reviews some of the problems in more detail.

4.3 Guidance/Standards

From a general internet search and personal communications, some examples of national guidance/standards for compounding have been identified and these are listed in Annex 3. Standards for Compounding/Formulation.

The level and detail of information included varies considerably between countries and standards in developing countries may be limited by lack of resources (including the availability of active ingredients and potable water or equipment), trained personnel and facilities. However, to varying degrees, the standards/guidance identified tend to include advice on expected standards for the following aspects of 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; and
- recall procedure.
4.3.1 Competency of staff involved in compounding

In the UK, the Royal Pharmaceutical Society and the British Pharmacopeia 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 should be covered by standard operating procedures and be fully documented.

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 (51) identified that only 10 African countries had more than 10 pharmacists per 100,000 population at that time. Whilst the International Pharmaceutical Federation (FIP) and WHO have encouraged national pharmaceutical associations in individual countries to decide what can be achieved in terms of good pharmacy practice (GPP), in many developing countries, national organizations are either non-existent or else too small to carry out such an exercise.

4.3.2 Formulation and stability

Much has been written on formulation and stability of compounded preparations (See Annex 4. Selected Bibliography).

Where there is a need to undertake compounding, 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 children’s hospitals and commercial small-scale manufacturers, quality assurance 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 Annex 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 potentially toxic ingredients and of calculation errors (52).
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® (Paddock Laboratories) which may not be generally available, especially in developing countries.

Compounding without suspending agents can cause patient harm. A recent report in the UK describes the compounding 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 (35).

A further issue to be considered in compounding is the need for antimicrobial preservatives and other 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, stabilizers 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 cosolvent, stabilizer 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 compounded formulations (15, 47, 53, 54, 55, 56) and these are useful for further information. In general, however, whilst the potentially problematic excipients are known, safe exposure limits for babies, infants and children have not been established (57).

Recommendation

WHO should seek to produce a list of excipients and safe exposure limits for babies, infants and children and a list of compounded formulations of common medicines that contain a minimum of excipients.

Examples of excipients which may pose problems for children are given in Annex 5. Examples of excipients that may be problematic for children.

4.3.3 Source and quality of ingredients

It is the responsibility of trained personnel (ideally a pharmacist) to ensure ingredients are 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. to meet with the specific requirements of a recognized pharmacopoeia) used in validated formulations. In any situation, steps should be taken to ensure satisfactory quality of any substance used in compounding by sourcing from approved and trusted suppliers. Ingredients should be identified and tested against recognized standards wherever possible.

It may be easier and safer to source authorized tablets and capsules than active chemical ingredients. The former are used with commercial or locally-produced suspending vehicles and many formulations have been published using vehicles such as Ora-Plus® and Ora-
Sweet® (Paddock Laboratories) (58). Care must be taken in extrapolating results of studies with particular brands of tablet/capsule and vehicle.

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 and bioavailability (59).

4.3.4 Site, facilities and equipment

All standards/guidance identified advise 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 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 developed countries standards require potable water to be supplied for hand and equipment washing and purified water must be used for compounding non-sterile drug preparations and for rinsing equipment and utensils.

4.3.5 Quality assurance

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).

UK and US 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.

It must be recognized that most compounded formulations have not been tested for bioavailability and that there is some evidence of variation between compounded formulations and authorized products and between different compounded formulations (60, 61). This may have clinical relevance, especially for drugs with a narrow therapeutic range.

4.3.6 Effective documentation

Records should be made and kept and 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 should also include the patient’s and prescription details and the date of dispensing. A record should be kept of personnel involved including the identity of the pharmacist taking overall responsibility.
A further objective of good documentation is to allow another operator 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.

4.3.7 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.

The product should 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; and
- name and address of patient.

4.3.8 Documented procedure for complaints and recalls of dispensed compounded products

If product deficiencies considered potentially harmful to health are identified, the product should be recovered as soon as possible. A written procedure for a recall should be in place (15).

Conclusion

Compounding preparations poses a high risk to patient safety and is generally subject to low levels of quality assurance. Adherence to standards for compounding is necessary to ensure safe preparation of good quality products.

Recommendation

WHO should take steps to standardize common compounded preparations to formulae for which there is good quality, efficacy and stability data and promote this information is to improve current practice.

Minimum pharmaceutical standards for compounding should be produced.

WHO should promote awareness of the potential problems when compounding and arrange education and training so that risk can be reduced.
ANNEX 1
METHODOLOGY

As well as using personal reference collection; NHS evidence, evidence-based reviews (including Bandolier, Cochrane, DARE, HTA Database), Medline, Embase and International Pharmacy Abstracts (IPA) were searched using the following strategies:

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; (open$ 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 result.
25. MEDLINE; (segment$ AND suppository).ti,ab; 10 results.
26. MEDLINE; (dose AND manipulation).af; 2066 results.

EMBASE

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/good practice

An invitation to provide information was placed on the E-drug discussion group website (http://www.essentialdrugs.org/edrug/) and was sent to personal contacts in children’s hospitals in various countries.
ANNEX 2
REFERENCES

17. Kairuz T et al. Extemporaneous compounding in a sample of New Zealand Hospitals:
22. USP-NF. General Chapter 905: Uniformity of Dose Units. US Pharmacopeia, Rockville, MD, USA.
34. Smyth JA (Ed). The NEWT Guidelines for administration of medication to patients


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


58. [www.paddocklabs.com].


ANNEX 3
STANDARDS FOR COMPOUNDING/FORMULATION

(for references see Annex 4. Section 4.11: Regulatory guidelines/reflection papers)

<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. Includes performance standards for common paediatric preparations</td>
</tr>
<tr>
<td><strong>EUROPE</strong></td>
<td></td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td></td>
</tr>
<tr>
<td>US Pharmacopeia USP29</td>
<td>Chapter 1075 Good Compounding Practices</td>
</tr>
<tr>
<td>US Pharmacopeia USP29</td>
<td>Chapter 795 Pharmaceutical Compounding – Non-sterile Preparations</td>
</tr>
<tr>
<td>US Pharmacopeia USP 29</td>
<td>Chapter 797 Pharmaceutical Compounding – Sterile Preparations</td>
</tr>
<tr>
<td>US Pharmacopeia USP29</td>
<td>Chapter 1160 Pharmaceutical Calculations in Prescription Compounding</td>
</tr>
<tr>
<td>US Pharmacopeia USP 29</td>
<td>Chapter 1163 Quality Assurance in Pharmaceutical Compounding</td>
</tr>
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<td>Country</td>
<td>Source/Text</td>
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<td>-------------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td></td>
<td>Practice of compounding is regulated and restrictions are imposed by the</td>
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<tr>
<td></td>
<td>Argentina Health Department. However, Argentina has few established</td>
</tr>
<tr>
<td></td>
<td>regulations to guide the daily compounding practices and the guidelines on</td>
</tr>
<tr>
<td></td>
<td>which pharmacies are regulated are based on outdated legislation.</td>
</tr>
<tr>
<td>AUSTRALIA</td>
<td>Pharmaceutical Society of Australia.</td>
</tr>
<tr>
<td></td>
<td>Professional Practice Standards, Standard 10: Compounding (also known as</td>
</tr>
<tr>
<td></td>
<td>Extemporaneous Dispensing). Version 4, 2010</td>
</tr>
<tr>
<td></td>
<td>Pharmaceutical Society of Australia</td>
</tr>
<tr>
<td></td>
<td>National Competency Standards Framework for Pharmacists in Australia, 2010</td>
</tr>
<tr>
<td></td>
<td>Oceania Health</td>
</tr>
<tr>
<td></td>
<td>Review of the need for further regulation of extemporaneous compounding.</td>
</tr>
<tr>
<td></td>
<td>January 2005</td>
</tr>
<tr>
<td></td>
<td>Practice of compounding is regulated by the Ministry of Health. The</td>
</tr>
<tr>
<td></td>
<td>compounding of pharmaceuticals, including non-prescription (over-the-</td>
</tr>
<tr>
<td></td>
<td>counter) medicines is permitted in Belgium and pharmacists are allowed to</td>
</tr>
<tr>
<td></td>
<td>compound every dosage form as long as some ‘forbidden’ active ingredients</td>
</tr>
<tr>
<td></td>
<td>are not used. However few pharmacists have a great interest in compounding</td>
</tr>
<tr>
<td></td>
<td>and those that do encounter problems in complying with new regulations.</td>
</tr>
<tr>
<td>BRAZIL</td>
<td>Personal Communication</td>
</tr>
<tr>
<td></td>
<td>ANVISA have a regulation (RDC 67/2007) that includes an annex VI that</td>
</tr>
<tr>
<td></td>
<td>describes the conditions needed to prepare unitary doses including</td>
</tr>
<tr>
<td></td>
<td>manipulation of dosage forms and other procedures needed to prepare</td>
</tr>
<tr>
<td></td>
<td>medicines for children, for administration via naso-gastric tubes, for</td>
</tr>
<tr>
<td></td>
<td>extemporaneous formulations and criteria for manipulation. Some Brazilian</td>
</tr>
<tr>
<td></td>
<td>public and private institutions prepare their own basic guidelines about</td>
</tr>
<tr>
<td></td>
<td>extemporaneous formulations</td>
</tr>
<tr>
<td>CANADA</td>
<td>Health Products and Food Branch Inspectorate, Health Canada</td>
</tr>
<tr>
<td></td>
<td>Policy on Manufacturing and Compounding Drug Products in Canada. POL-0051,</td>
</tr>
<tr>
<td></td>
<td>January 26th 2009</td>
</tr>
<tr>
<td></td>
<td>Canadian Society of Hospital Pharmacists</td>
</tr>
<tr>
<td></td>
<td>Non-sterile Compounding: Guidelines for Healthcare Facility Pharmacies, 1992</td>
</tr>
<tr>
<td></td>
<td>Canadian Society of Hospital Pharmacists</td>
</tr>
<tr>
<td></td>
<td>Boggio L. Chair, Working Group to Examine Pharmacy Compounding</td>
</tr>
<tr>
<td></td>
<td>Guidelines for Compounding Preparations. Pharmacy Connection, July/August</td>
</tr>
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<td></td>
<td>2006: 18-21</td>
</tr>
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<td>Country</td>
<td>Source</td>
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</tr>
<tr>
<td>COLOMBIA</td>
<td>International Journal of Pharmaceutical Compounding, 2008; 12(2): 107</td>
</tr>
<tr>
<td>ESTONIA</td>
<td>Personal Communication</td>
</tr>
<tr>
<td>GERMANY</td>
<td>Personal Communication</td>
</tr>
</tbody>
</table>
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.

**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.nl](http://www.knmp.nl)
### ITALY

**Personal Communication**

Italian Society of Hospital Pharmacy has recently produced a manual of guidelines covering extemporaneous preparations. Italian regulations allow the compounding 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. 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 laboratory. Complete guidelines for every pharmaceutical preparation are available to pharmacists and technicians for the correct and safe production of formulations.

### MEXICO


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.

### NEPAL

Nepal Pharmacy Council

**National Good Pharmacy Practice Guidelines, 2005.** Includes brief guidance on compounding or extemporaneous dispensing – formulae, quality of ingredients, equipment, containers, records.

### NEW ZEALAND

Pharmaceutical Society of New Zealand

**Competence Standards for the Pharmacy Profession.** The Pharmaceutical Society of NZ, 2002

Ministry of Health

New Zealand Pharmaceutical Schedule. Wellington: Ministry of Health 2006

<table>
<thead>
<tr>
<th>Country</th>
<th>Source</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMAN</td>
<td>Sultan Qaboos University Hospital. Personal Communication</td>
<td>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.</td>
</tr>
<tr>
<td>POLAND</td>
<td>Personal Communication</td>
<td>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.</td>
</tr>
<tr>
<td>PUERTO RICO</td>
<td>International Journal of Pharmaceutical Compounding, 2008; 12(2): 110-111</td>
<td>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 non-sterile formulations and USP Chapter 797 for sterile formulations.</td>
</tr>
<tr>
<td>SOUTH AFRICA</td>
<td>Personal Communication</td>
<td>In South Africa the right of pharmacists to compound is entrenched in the Medicines Act. Good Pharmacy Practice in South Africa, 3rd Edition, 2008. Includes a brief section on compounding</td>
</tr>
</tbody>
</table>
### SWITZERLAND

| Personal Communication | Follow Good Manufacturing Practice in the Pharmacopoeia Helvetica which is obligatory for preparing small amounts of medication in hospital pharmacies. A guideline 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 |

### SUDAN


### ZIMBABWE

| Personal Communication | No specific national or local instructions or guidance on manipulation of doses or extemporaneous preparation in Zimbabwe from regulators or from the 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. |
ANNEX 4
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4.1  Formulation and stability


http://homepages.paradise.net.nz/alanmcc/Paradise/eMixtdemo/DWoods/index.html

Bethesda, MD: ASHP; 2003.


USP Compounding Backgrounder  

Woods DJ. Extemporaneous formulations of oral liquids – a guide  

4.2  Administration through enteral tubes

Smyth JA. The NEWT Guidelines for Administration of Medication to Patients with Enteral Feeding Tubes or Swallowing Difficulties. 1st Edition.

Pharmaceutical Press.

4.3  Alternatives to compounded preparations

Anon. Academic detail aid for prescribers – choosing medicines for patients unable to take solid oral dosage forms. UKMI, January 2010.
4.4 Problems with compounding/manipulations


Rosenberg JM, Nathan JP, Plakogiannis F. Weight variability of pharmacist dispensed split tablets. J Am Pharm Assoc 2002; 42(2): 200-0.5


4.5 Regulatory guidelines/reflection papers


4.6 Excipients


4.7 Reports


4.8 Presentations


4.9 Reviews


4.10 Palatability


4.11 Standards for compounded preparations

Allen LV. A series of articles on many aspects of compounding/extemporaneous dispensing. Secundum Artem volumes 1-16 available under ‘Resources and Education’ at http://www.paddocklabs.com/.


Fenton-May V’I (ed). Guide to the Preparation of Non-Sterile Extemporaneous Products. Cardiff: Regional Pharmaceutical QC Committee; 2003 - no longer readily available; much of the information is incorporated into


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


4.12 Paediatric Formularies


4.13 Miscellaneous


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


### ANNEX 5
### EXAMPLES OF EXCIPIENTS THAT MAY BE PROBLEMATIC FOR CHILDREN

<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 diarrhoea</td>
<td>No information</td>
</tr>
<tr>
<td>Flavouring agents / colourings</td>
<td>Allergic and adverse effects</td>
<td></td>
</tr>
</tbody>
</table>
ANNEX 6
GLOSSARY

Age-appropriate formulation/dosage form
A dosage form considered (by health-care professionals and carers) suitable for the age and ability of the child.

Compounding
The US Pharmacopeia 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
This is poorly defined. A working definition in the context of this paper 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" (see Brion F et al (7)). However, extemporaneous preparations may also be prepared from authorized dosage forms and commercial or locally-produced suspending agents rather than from individual chemical ingredients.

In this paper the term "compounding" has been preferred to "extemporaneous dispensing or preparation".

Label/labelling
The authorization to market a product in the USA is contained on the "label" (or labelling) approved by the FDA.

Magistral
Term used in European medicines regulations to describe a medicine prepared to the special requirements of a patient following the prescription of a doctor (see also "Officinale").

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
In the context of this paper, manufacturing is taken to mean the preparation of medicines in authorized facilities to the standards of good manufacturing practices. The medicines will usually have a marketing authorization, product licence or other regulatory approval. In some countries facilities may be authorized to manufacture medicines to these standards even
though the medicine does not have full regulatory approval (in the UK these unlicensed medicines are known as "specials")

**Marketing authorization**
The authorization to market a product in Europe is contained in the marketing authorization 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 authorization (EU) (e.g. rectal paraldehyde, sublingual lorazepam, buccal midazolam using the injection solution). Medicines which are "authorized" in one country may be "off-label" in another because authorization procedures are often not harmonized between countries.

**Officinale**
Term used in European medicines regulations to describe a medicine prepared to the formula of an official pharmacopeia (see also "magistral").

**Special**
A drug product in the UK which does not have a marketing authorization but has been produced to the quality standards of good manufacturing practices by a manufacturing unit licensed for such production. Whilst there may be assurances of quality and safety, efficacy and bioavailability have often not been studied.

**Therapeutic index**
The ratio between the therapeutic dose and the dose producing adverse effects or toxicity. Drugs with a "narrow" therapeutic index include gentamicin and phenytoin.

**Unlicensed**
A drug that does not have an authorization from the regulatory authority of the country in which it is being used. The drug may be authorized in another country or may have been compounded.
ANNEX 7

COMPOUNDING FORMULATION – CONSIDERATION OF THE POTENTIAL PROBLEMS

If an alternative to compounding or 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. Added ingredients or excipients may not be appropriate for babies and infants, e.g. ethanol, propylene glycol. 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 a compounded 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 compounded oral liquids should only be used for a maximum of one month from the date of preparation to minimize any unrecognized 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 but there is little supporting evidence for the recommendation.

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

Chemical instability
Drugs in compounded liquids may be susceptible to chemical reactions leading to degradation. The most common reactions are hydrolysis, oxidation and reduction. 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. Other factors which may increase the rate of reaction include the presence of trace metals which catalyse the oxidation of captopril, methyldopa or exposure to light which catalyses the oxidative degradation of 6-mercaptopurine. The rate of chemical degradation usually increases with temperature, 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.

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 (i.e. suspensions), thus suspensions of acetazolamide and chlorothiazide are more stable than solutions. However, it cannot be assumed in all cases that a compounded suspension is more stable than a solution. In a suspension, 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. Furosemide 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.

Microbiological instability
Microbial growth in an oral liquid may cause a foul odour and turbidity and adversely affect palatability and appearance. High titres of microorganisms may be hazardous to health especially in very young or immunocompromised patients. By-products of microbial metabolism may cause a change in the pH of the preparation and reduce the chemical stability or solubility of the drug. Microbial contamination during preparation must be minimized 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 unionized form is predominant. 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**

Compounded oral suspensions may be susceptible to sedimentation of insoluble drug causing caking. Difficulty in resuspending the drug or rapid sedimentation following shaking can lead to erratic dosage measurement as demonstrated with chlorothiazide suspension and this inherent problem with compounded formulations is of considerable concern. Some spironolactone suspensions have been reported to be excessively thick and almost unpourable. Refrigeration, whilst usually desirable to maximize chemical stability and reduce microbial growth, can also increase the viscosity of a suspension making resuspension 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.

**Medication error potential**

There have been many examples of medication error when compounding preparations and some have resulted in serious harm to patients or death. The potential for medication error must be recognized and steps taken to minimize the risk. This will include as a minimum the use of a worksheet listing the formulation ingredients and the identity of ingredients, quantities and calculations, and measurements should be double-checked by trained personnel and signatures provided. The pharmacist responsible should check the final product and label against the signed worksheet, ingredients and prescription.
ANNEX 8
PRACTICAL EXAMPLES

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

Background
No therapeutic alternative considered desirable. Vigabatrin preferred.

No oral liquid available and no information on compounded 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 ongoing need is anticipated investigate source and supply of Vigabatrin Sachets
Information in Martindale, other standard texts or internet search state that Vigabatrin is freely 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.

N.B. Even though the entire 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 is 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.

ACE inhibitors

A. Captopril
A dose of captopril 11 mg twice daily is ordered for an infant. The prescriber requests an oral liquid to be made.

Background
Captopril liquid is available in some countries but there is no local supply

Captopril liquid can be compounded but the required formulation ingredients are not available.
Tablets of 25 mg are available and these are scored into quarters.

Captopril is very soluble in water.

**Action**
A dose modification is discussed with the prescriber and it is decided that giving 12.5 mg twice daily instead of 11 mg twice daily is not clinically significant. This allows half a tablet (12.5 mg) to be given dispersed in water or juice just prior to administration.

This should give a reliable and reproducible dose especially as the drug will be in solution.

**B. Enalapril**
Enalapril is requested for an infant.

**Background**
There is no commercially available liquid.

Enalapril liquid can be compounded but the required formulation ingredients are not locally available.

Enalapril maleate is soluble in water but the tablets available are film-coated and difficult to break and disperse.

**Action**
An alternative is to convert the required dose to the equivalent of Captopril and follow the process in A above.

**Calcium channel blockers**
A small dose of nifedipine is prescribed for an infant to be given three times a day.

**Background**
Extended-release nifedipine capsules cannot be crushed and there is no information on a compounded formulation.

Liquid-filled gelatine capsules are available and it is suggested that an amount of liquid corresponding to the dose can be removed with a needle and syringe and then given to the infant. However, this method is not accurate and is a difficult and potentially hazardous manipulation.

**Action**
A therapeutic alternative is Amlodipine. Its long half-life means that it can be given once daily instead of three times a day. An equivalent dose is calculated.

Amlodipine is very soluble in water and tablets or accurately prepared tablet fractions can be dispersed in water, giving a solution of the drug. If the Amlodipine tablet is dispersed in a known volume of water an aliquot corresponding to a fractional dose can be measured.

Information on a compounded formulation has been published which may be an option if treatment is long-term and if the formulation ingredients are available.
Dexamethasone
Dexamethasone oral liquid is required to dose a new born baby.

Background
An oral liquid is made in some countries but is not immediately available. There are no other liquid corticosteroid preparations available.

Tablets do not disperse well and the drug is very insoluble making the measurement of a fractional dose very difficult and potentially risky.

A search of the literature finds that dexamethasone sodium phosphate injection has been used to prepare an oral liquid diluted in Ora-Plus/Ora-Sweet commercial bases. Whilst these bases are not available, this information indicates that giving the injection orally could be an option, especially as treatment is likely to be short-term.

Action
Dexamethasone sodium phosphate can be given orally by measuring out the required amount from a rubber-stopped vial with a needle and syringe. The measured liquid can then be mixed with a juice or flavour if necessary. You check that the dose required can be measured accurately without further dilution.

Action
From your literature search you note that dexamethasone injection containing metabisulfite has been linked to neurotoxicity and you discuss potential risks with the neonatologist and check that the brand you are using does not contain metabisulfite.

N.B. Whilst there are preservatives in the multidose injection vial, they are very similar to those in commercial bases, so should not pose any harm unless it is known that the infant is hypersensitive to any of the components of the injection.

The injection vial could be used for multiple oral doses but it should be clearly labelled to prevent inadvertent parenteral administration.

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