MAGISTRAL PREPARATIONS

INTRODUCTION

- Pharmacists are responsible for ensuring that drug use is safe and effective.
- Wherever practicable, licensed medicines are used and represent the ‘gold standard’ for quality, safety and efficacy. There are, however, circumstances in which there is no licensed medicine that fully meets the clinical needs of a particular patient or patients. In these circumstances it is sometimes necessary for the pharmacist to extemporaneously prepare a limited quantity of a custom-made medicine for a specific patient.
- Oral liquid medicines are commonly extemporaneously prepared because of a relative lack of licensed formulations for groups such as the young or elderly who are unable to swallow tablets or capsules, or for whom the required dose is less than a single tablet/ capsule.

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- Extemporaneous preparation remains one of the highest risk preparative activities carried out in the pharmacy, as the risks of unlicensed medicines are combined with inherent risks associated with the pharmaceutical compounding process
- In addition, extemporaneously prepared medicines are commonly given to some of the most vulnerable patients in hospitals and communities (e.g. neonates, children, elderly patients, stroke victims, patients with feeding tubes in situ).
- These vulnerable patients are often not capable of alerting carers or staff to any adverse drug events they may be experiencing.

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- There have been a number of reports of errors associated with the use of extemporaneously prepared medicines, resulting in serious harm to patients.
- The most notable incident in recent UK history was the ‘peppermint water case’, where the use of the wrong strength of chloroform water led to the death of a child.
- This case highlighted the issues of toxic ingredients and calculation errors, particularly where the strength of one or more ingredients is stated in a historical or non-standard fashion.
- Similar incidents have occurred in the USA, including the death of a child from a superpotent imipramine liquid, and another of a 5-year-old child who received a thousand-fold overdose of clonidine

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- Administration errors have also been reported, including five-fold, tenfold, hundred-fold or thousand-fold mistakes in calculating or measuring doses.
- Some of these errors have been attributed to inadequate labeling (e.g. confusion between strengths expressed per mL or per 5 mL).
- The relative lack of research and development work supporting these products is associated with the potential for formulation failure or poor dose uniformity, resulting in the risk of overdose or underdose.
- The lack of high quality data to support historical formulae has been acknowledged by authors across the world

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- Even where a given formulation has been shown to achieve suitable physical, chemical and microbiological stability, the bioavailability and palatability of the preparation may be unproven.
- Very few extemporaneous preparations are supported by any data to demonstrate a suitable absorption profile and/or bioequivalence with a licensed preparation.
- Other issues include concerns about inadequate access to equipment and materials needed to provide a safe extemporaneous dispensing service and the highest possible quality products
- There is therefore an identified need to investigate and improve the quality of formulation of the oral medicines currently prepared, with a view to offering further guidance to pharmacists in order to minimize risks to patient safety.

PREPARATION

- The preparation process includes all the practical procedures and processes required to extemporaneously prepare, package and label a medicine, ready for supply to a named patient.
- Critical processes in the preparation of extemporaneous products should be identified using process mapping techniques.
- Critical processes include the following:
- * prescription verification
- * worksheet and label generation
- * assembly of components
- * weighing
- * measurement of liquids
- * grinding tablets into uniform powders
- * mixing
- * reconciliation
- * packaging and labeling.
- Appropriate control measures should be implemented at all critical points in the process and should include a procedural check (independent, wherever possible) by a suitably trained person as a minimum.
- These measures should be validated (in the case of reproducible or automated processes) or subject to competence assessment (in the case of operator dependent processes).

PREPARATION

- **Prescription verification**

All prescriptions must be signed by an approved prescriber.

Prescriptions should be clear, unambiguous and accurate. The medicine(s) and dose(s) selected must be appropriate to meet agreed therapeutic objectives.

Pharmacists should ensure that medication errors do not occur from any cause, including as a result of prescribing, formulation or calculation errors.

It is the responsibility of the authorizing pharmacist to ensure that prescriptions are verified.

PREPARATION

- **Prescription verification**

A written approved procedure should be in place for prescription verification which should include checks for the following where appropriate:

* full signature of authorized prescriber and date

* patient details (e.g. full name, hospital number, consultant, ward, date of birth, weight where appropriate).

* correct dose calculation

* administration details

* compatibility with prescribed constituents

* stability of formulation

* correct presentation for intended route of administration

* absence of contraindications, allergies or drug interactions.

Records must indicate who carried out the verification of each prescription.

These records should be retained for a period that is in accordance with legal requirements and with the local policy.

PREPARATION

- **Documentation**

The relevant master document should be selected and a product specific worksheet and label should be prepared before starting preparation.

Where a calculation is required, it should be independently checked by an appropriate second person wherever possible.

The check should be performed prior to preparation to minimize the chance of product wastage.

PREPARATION

- **Starting materials**
- All starting materials should be checked against the worksheet to ensure that the correct materials have been selected.
- Ensure that all starting materials are either licensed or have been approved for use following a quality assessment.
- The chemical and microbiological quality of any water used in preparations should be specified and monitored if taken from the mains or local water systems. Monitoring is not necessary if sterile bottled water for injections or irrigation is used.
- Sterile bottled water should be given a maximum shelf-life of 24 hours once opened, with its status clearly labeled.
- Ensure that the starting materials are ‘in date’ at the time of production and for the duration of the product’s shelf-life.
- Check that containers are clean and fit for use.

PREPARATION

- **Weighing**
- Before starting the process, ensure the weighing range of the balance is appropriate for the quantity of material to be weighed.
- The balance should be leveled according to the leveling bubble (where appropriate) and should be protected from draughts and risk of other disturbance.
- The balance should be checked regularly using appropriate weights and be re-calibrated if necessary.
- Records of checks and calibrations should be maintained.
- Where possible the balance should be linked to a printer so that a permanent record of the weight measured can be retained with the worksheet

PREPARATION

- **Weighing**
- Record accurately the batch number and expiry date of the starting materials on the worksheet.
- Check that the balance is weighing the correct units of weight (micrograms, milligrams, grams, kilograms, etc.).
- Before commencing weighing, the balance should be tarred.
- Where possible, a second person should check that the correct materials and weights of material have been used and measured.
- This should be recorded on the worksheet.
- Common errors in weighing to look out for include:
- * putting the decimal point in the wrong place (e.g. 14.4 g instead of 1.44 g)
- * reversing the order of digits (e.g. 15680 g instead of 15860 g)
- * misreading double digits 14556 g instead of 14566 g).

PREPARATION

- **Measurement of liquids**
- The measuring of all liquid starting materials should be undertaken in appropriate and validated measuring vessels wherever possible.
- In some cases the use of unvalidated devices may be appropriate (e.g. syringes for small volumes).
- The selected measure should be appropriate for the volume of liquid required.
- Where possible, glass measures should be avoided to minimize the risk of undetected contamination with broken glass.
- When glass is used, it should be regularly inspected for chips and cracks and replaced as necessary. It is recognized that in some cases glass may be the container of choice (e.g. when measuring oils and solvents).

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- **Crushing tablets**
- 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 uniformity.
- Tablets should be ground to a powder using a pestle and mortar, and a check of powder uniformity should be made and documented on the worksheet

PREPARATION

- **Mixing**

1. **Powders**

Where two powders are to be mixed, the process should be undertaken in a way that will achieve homogeneity. This is commonly accomplished by triturating equal aliquots of the powders, mixing well between each addition, until the entire quantity of the bulk material has been incorporated

2. **Liquids**

Miscible liquids will eventually mix completely by diffusion. To speed up the

process the liquids should be mixed using a stirring rod or paddle. Avoid the use of glass stirring rods or stainless steel stirring rods in glass containers, as this can increase the risk of contamination with glass fragments.

Where powder is to be dissolved in or added to a liquid to make a solution or suspension, it should be added to the liquid slowly with continuous stirring to prevent it from aggregating. Once the powder is dissolved or evenly dispersed, the solution should be made up to the required volume.

PREPARATION

- **Mixing**

3. Semi-solids

The final product should always be uniform in appearance and consistency.

Where a dispersion of particles or solution into a semi-solid is required (e.g. ointment, cream, paste), a small amount of the semi-solid should be mixed with the powder/liquid to form a stiff paste before incorporating the remainder of the vehicle, in small aliquots, to form a homogeneous product.

Where a mechanical mixer is used to assist in the preparation of a semisolid product, consideration should be given to the optimum mixing period, as too short or too long a time may have detrimental effects on the final product

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- **Packaging and labeling**
- The primary packaging for the product (e.g. bottle and closure) must be fit for purpose. It must adequately protect the product from the environment while being compatible with the product.
- The physico-chemical properties of the drug and formulation should be considered when selecting the type of packaging.
- * For medicines sensitive to light, a light-proof pack should be considered (e.g. opaque or amber bottle).
- * When a medicine is sensitive to oxidation, a tight-fitting closure and impermeable pack is required.
- * The potential for medicine loss by absorption and permeation, or leaching of additives from plastics needs to be considered for certain formulations (e.g. poorly soluble medicines formulated with solvents to improve drug solubility).

PREPARATION

- **Packaging and labeling**
- Generally glass can be considered to be inert and can be universally used as a container for the vast majority of formulations (with the exception of some concentrates, e.g. sodium bicarbonate).
- Labels should be clear and legible, and must comply with all the statutory and professional requirements.
- The information on the label should reflect the product prepared, and should tie in with the master label on the worksheet.
- Where possible the contents of the label should be independently checked against the worksheet and the prescription/requisition.

Finding and choosing an appropriate formulation

- As with clinical papers, the pharmacist must consider the quality of the evidence source and the overall appropriateness of the formulation.
- Comprehensive data should include information on physical and microbiological stability, as well as chemical stability testing. In rare cases, a given formulation may also be supported by successful clinical outcome data.
- When choosing a formulation, it is imperative to consider the holistic needs of the prospective patient. This includes decisions regarding the form, strength, viscosity and excipient content of any given formula.
- For example, a formulation designed for use in adults may contain inappropriate excipients for use in a child, and a viscous suspension may not be suitable for administration via a nasogastric tube.
- Furthermore, historical formulations may contain starting materials which are no longer considered to be appropriate (e.g. chloroform).

Hints on choosing a formulation – things to consider

1. Shelf-life

- Given the risks associated with extemporaneous formulation, it is recommended that the shelf-life of any extemporaneous product should not exceed 28 days if preserved or 7 days if unpreserved.
- In the absence of supporting data, a limited shelf-life should be assigned based on the risk assessment of the individual drug.
- For drugs with narrow therapeutic indices, this may be as little as 2 or 3 days

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