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Risk management

2.1 Introduction

The extemporaneous preparation of medicines is associated with a number of potential risks to patients, healthcare staff and their organisation. These all need to be carefully considered in determining the best treatment option; they then need to be minimised when the use of this category of medicine is necessary. A risk assessment should be performed before making a decision to extemporaneously prepare a medicine in line with the local unlicensed medicines policy. This process should be underpinned with a procedure in place and records of risk assessments should be maintained on file.

This section gives guidance on the risks associated with extemporaneous preparation, the assessment and management of these risks and alternative options to extemporaneous preparation.

2.2 Legal background and organisational risks

Medicines legislation requires that medicinal products are licensed before they are marketed in the UK. Accordingly no medicinal product may be placed on the market without a marketing authorisation.

The marketing authorisation provides assurance of the safety and efficacy of the drug in relation to a specified use, which has been reviewed and accepted by an official expert body. It also defines the legal status of the product and assures its quality. A marketing authorisation specifies the clinical condition(s), dose(s), routes of administration, and packaging for the particular preparation, all of which are detailed in the Summary of Product Characteristics (SPC).

Extemporaneously prepared medicines are unlicensed medicines and are not subject to these regulatory safeguards. Therefore neither prescribers nor pharmacists can make the same assumptions of quality, safety and efficacy about these products as they do for licensed medicines.

It should also be noted that the extemporaneous preparation of medicines from licensed starting materials (e.g. tablets, capsules, injections)

also removes these regulatory safeguards unless specifically covered in the SPC. It is therefore an area of pharmaceutical activity which carries potentially increased risk to the patient, the supervising pharmacist and any other healthcare professionals involved in preparation and/or administration.

The pharmacist responsible for preparing or procuring an extemporaneously prepared medicine should therefore take responsibility for ensuring that the medicine is of suitable quality, and is safe and efficacious. A failure to do so puts both the pharmacist and organisation at risk in terms of both civil liability (negligence, breach of contract: Sale and Supply of Goods Act 1974) and criminal liability (Medicines Act 1968, Health and Safety at Work Act 1974, Corporate Manslaughter and Corporate Homicide Act 2007, Consumer Protection Act 1987). The pharmacist should also ensure that the prescriber is aware of the unlicensed status of the medicine and any associated risks with its use.

Extemporaneous preparation should therefore only be considered when an equivalent licensed product is unavailable or is unsuitable for use and if the use can be clearly justified clinically and pharmaceutically. Consideration should be given to all alternatives before choosing this option.

However, it is recognised that some patients may have special clinical needs that cannot be met by licensed medicinal products or by a viable alternative option. In these circumstances it would be inappropriate to curtail the patient's treatment, as this would have a detrimental effect on their condition. Whenever carrying out a risk assessment, the risks of not treating the patient should also be considered and be at the forefront of the decision-making process.

2.3 Alternatives to extemporaneous preparation

There are a number of alternative options that should be carefully considered as part of a patient-specific clinical risk assessment before opting for extemporaneous preparation. Each option has its own associated merits and risks, and the best option will vary according to specific circumstances surrounding both the patient's condition and the urgency of commencing the treatment.

2.3.1 Therapeutic substitution

The use of a licensed medicine from the same therapeutic classification should be considered and may provide a better clinical option than the use of an extemporaneously prepared medicine which has limited data to support its formulation and stability. However, the decision to switch to a different

medicine should also take into account the condition of the patient and the relative toxicity of the drug. For example, if a patient is stabilised on a medicine with a narrow therapeutic index, it may have a more detrimental impact on the patient's well-being to switch to a different, but therapeutically equivalent drug, than use a medicine that has been extemporaneously prepared against a validated formulation. However, in either case, the patient should be closely monitored following the change to their treatment to ensure their condition remains under control.

The use of a less potent steroid rather than diluting a potent agent is an example where a therapeutic alternative may eliminate the need for an extemporaneous preparation.

The use of an alternative route of administration, for example use of the rectal rather than the oral route, could also be considered if an appropriate formulation is available.

2.3.2 Procurement options

2.3.2.1 *Use of an imported product*

The importation of a suitable product that carries a marketing authorisation in its country of origin should be considered. However, it must be noted that the presence of a non-UK marketing authorisation confers no legal status on the medicine in the UK and that importation can only take place through a company holding a Wholesale Dealer (Import) Licence.

The preparation selected should be licensed for use in a country with equivalent or similar licensing arrangements and regulatory standards to the UK (e.g. EU, Canada, Australasia). This will provide the requesting pharmacist with assurance that the quality, safety and efficacy of the medicine have been reviewed by a competent regulatory authority. However, care should be taken to ensure that the medicine has been licensed for use in the country of origin and placed on the market there, rather than being manufactured solely for export.

The procuring pharmacist should also ensure that the company used for importation has adequate quality systems in place to ensure that the medicine comes from a reputable source; that counterfeit detection measures are in place; and that the cold chain (where appropriate) is maintained to the point of delivery (see Chapter 11 for more details).

From a clinical perspective, the procuring pharmacist needs to be aware that if the medicine is being used outside of its intended purpose, the safety and efficacy review may not apply to their specific clinical indication. Therefore it is important that the procuring pharmacist reviews the SPC and patient information leaflet (PIL) to ensure that they are appropriate for the intended use and provide alternative guidance if necessary.

Patient information, user guidance and the label must include comprehensive, relevant information in English. When importing a product from a non-English-speaking country, provision must be made to ensure that the product is labelled appropriately and that sufficient guidance is provided to the clinician and patient to ensure safe use.

When importing borderline substances such as vitamins and food supplements, preference should be given to procuring products that have been marketed as medicines wherever possible. Where this is not possible, a quality assessment should be carried out to ensure that the product is free from transmissible spongiform encephalopathies (TSE) as a minimum.

2.3.2.2 *Use of a 'Special' manufactured in a MHRA-licensed unit*

The commissioning of a suitable preparation from a licensed 'Specials' manufacturer within the UK should be considered. The benefit of purchasing a 'Special' is that the product should be made to a validated formula with supporting stability data in accordance with the principles of good manufacturing practice (GMP). Licensed 'Specials' units are regularly inspected by the Medicines and Healthcare products Regulatory Agency (MHRA) to ensure these principles are upheld. However, the purchasing pharmacist will still need to review the supporting documentation (e.g. specification, Certificate of Analysis/Conformity, TSE statement) to assess whether the product is of appropriate quality.

Information on Specials manufacturers is available in the British National Formulary (BNF).

Guidance relating to the procurement of extemporaneously prepared patient-specific doses from 'Specials' manufacturers can be found in Chapter 11.

Further guidance for assessing the quality of both imports and 'Specials' can be found in the NHS Pharmaceutical Quality Assurance Committee guidance document 'Guidance for the purchase and supply of unlicensed medicinal products' (NHS Pharmaceutical Quality Assurance Committee, 2004). Advice can be sought from medicines information centres, regional quality assurance specialists, licensed importers of medicines and individual 'Specials' units.

2.3.3 **Practical options**

2.3.3.1 *Use of soluble or dispersible tablets*

Soluble or dispersible tablets may be a useful and convenient alternative to preparation of liquid extemporaneous products. Some tablets can be

dispersed, even if this is not within the terms of their marketing authorisation (licence). Most tablets will disperse in a small volume of water (~ 10 mL) within a few minutes. This practice presents fewer health and safety risks than crushing tablets, which can expose the carer to potentially harmful dusts via inhalation.

When dispersing tablets, the dose should be prepared and administered immediately, as stability cannot be guaranteed. It should be noted that slow or modified release preparations should not be used in this manner.

Care should be taken, however, if part doses are required. The practice of taking aliquots from insoluble, dispersed tablets for smaller doses presents a significant risk of dose inaccuracy. This is because water has no suspending properties, commonly resulting in aggregation and sedimentation of the drug, leading to poor dosage accuracy. For this reason, tablet dispersion may not be a practical option in paediatrics where the required doses are frequently fractions of the lowest available strength tablet.

2.3.3.2 *Cutting tablets*

The use of tablet cutters can sometimes provide an acceptable option, especially when tablets are effectively scored and designed to help in the administration of part doses. However, tablets cannot be cut with great accuracy of dose and research suggests that the variability may range from 50% to 150% of the desired dose even when using commercially available tablet cutters (Breukreutz *et al.*, 1999; Teng *et al.*, 2002).

2.3.3.3 *Use of a preparation intended for a different route*

The use of a suitable preparation intended for a different route of administration can sometimes be a practical alternative; for example the use of an injection solution orally, or an oral solution rectally. However, this practice has its own inherent risks and the pharmacist should ensure that the presentation used will be absorbed by this route and that it will be tolerated by the patient.

When using an injection by the oral route, consideration should be given to the possibility of rapid absorption and elevated peak levels, the potential for rapid drug degradation due to exposure to gastric acid and problems with first-pass metabolism. The pH of an injection should also be considered, as extremes of pH can adversely affect the gastric mucosa.

Some consideration should also be given to other excipients in the formulation such as propylene glycol and ethanol, which may be problematic if large volumes of the injection are required to provide the dose.

2.4 Risks associated with extemporaneous preparation

The technical and clinical risks associated with extemporaneously prepared medicines are considered below.

2.4.1 Formulation failure

All formulae used for extemporaneous preparation should be validated and have supporting stability data. Suitable sources include pharmacopoeial formulations, industry-generated expert reports and published papers.

However, it is recognised that there is a lack of standardised formulae available, leading to a plethora of different approaches and formulations being used which are commonly not peer reviewed or published. There are a number of risks associated with the use of non-standard formulations that need to be considered before taking this option.

Formulation failure can occur when a formulation has not been adequately validated, potentially resulting in either under- or overdose and associated toxicity or therapeutic failure. If a poorly formulated medicine that lacks dose uniformity is used, both underdosing and overdosing may occur during a course of treatment.

The causes of formulation failure are numerous and can be complex, including physical incompatibilities, drug/excipient binding issues and drug degradation. Generally, as the complexity of the formulation increases so does the risk of problems occurring. Formulations should therefore be kept as simple as possible for these reasons.

Oral liquids are usually formulated as either a suspension or solution. Solutions have the benefit of ensuring uniformity of dose, but drugs are more susceptible to degradation in solution than in the solid state and this should be considered when preparing a solution.

An insoluble drug suspended in a suitable vehicle may be less susceptible to drug degradation, but may settle out of the suspension over time, leading to sedimentation and caking. In this state, there will be a higher concentration of drug at the bottom of the bottle than at the top. If taken, this will result in the patient being underdosed at the beginning and overdosed towards the end of a treatment course. In order to ensure uniformity of dose, these formulations need to be shaken properly before use and patients need to be adequately counselled.

The majority of liquid formulations are prepared for children where small doses are required. In a number of cases, even suspended 'insoluble' drugs will be partially soluble at these concentrations and therefore it is important to review drug stability data and solution kinetics when assessing the formulation.

It should also be noted when using tablets as starting materials in the preparation of oral liquids that many of the excipients will be insoluble, even if the drug is soluble. These excipients can bind some of the drug and therefore it is prudent to use a suspending agent as the drug vehicle to ensure uniformity of dose. For this reason, filtration of this type of preparation should not be carried out.

2.4.2 Microbial contamination

Microbial contamination can pose a significant risk to immunocompromised patients, while by-products of microbial degradation can lead to physical or chemical changes in the preparation. Microbial growth can lead to spoilage, affecting product appearance and producing foul odours.

The choice of preservative for a formulation needs to take into account a number of factors including pH, physical compatibility and the intended patient group. Unpreserved preparations should be stored in a refrigerator and assigned a short shelf-life to limit microbial growth. A maximum shelf-life of 7 days at 2–8°C should be assigned to unpreserved oral liquid preparations unless sufficient validation work has been carried out to support an extended shelf-life.

2.4.3 Calculation errors

Calculation errors pose the greatest risk of causing serious patient harm 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 worksheet.

Common calculation errors associated with extemporaneous preparation include errors when converting units from one to another (e.g. milligrams to micrograms, conversions from weight in volume to millimoles).

Problems can also arise when doses can be prescribed as free base or salt, leading to potential calculation errors when making and administering preparations (e.g. two-fold errors if caffeine citrate is confused with caffeine base).

Care should be taken when diluting concentrates; calculation errors have been known to lead to 1000-fold overdoses (Kirsch, 2005).

Decimal point errors are commonplace and extra vigilance is needed to ensure that documentation is clear (especially worksheets and formulations) and that products are labelled without using decimal points wherever possible (e.g. 0.5 g should be labelled as 500 mg). Guidance relating to reducing the risk of medication errors can be found in Chapter 6.

Errors have also occurred when unfamiliar terminology is used to describe the strength of solutions and this was highlighted in the ‘peppermint water’ case (Anon, 1998) where concentrated chloroform water was used instead of double strength chloroform water, resulting in the death of a child.

2.4.4 Starting materials

The use of some historical formulae carries the associated risk of using ingredients that are no longer suitable. For example, chloroform has now been recognised as a class III potential carcinogen and is present in a number of old BP monographs (CHIP3 Regulations, 2002).

The toxicity of some ingredients is age-specific and they may be inappropriate for children, and some ingredients are unsuitable for certain religious groups (e.g. phenobarbital elixir (BNF) contains 38% alcohol). Alcohol has been linked to CNS-depressant and hypoglycaemic effects (Woods, 1997). Care should also be taken with the use of cariogenic sugars (e.g. sucrose) in paediatric formulations as it has been associated with dental cavities. It is therefore important to list all such excipients on the product label so that end-users are made aware of their presence in the formulation

All starting materials, particularly those of animal origin (e.g. gelatin) should be certified free from TSE.

2.4.5 Patient acceptability issues

Consideration should be given to the palatability and presentation of oral liquid medicines as there is a good argument that taste is crucial to achieving good compliance in children, especially for the treatment of longstanding conditions such as in cardiology.

2.4.6 Health and safety risks

The risks to the operator should also be considered. A Control of Substances Hazardous to Health (COSHH) risk assessment should be carried out and any risks should be identified and carefully evaluated before undertaking an extemporaneous preparation. (Note: once performed, this assessment does not have to be repeated each time the preparation is made, provided the assessment is up to date and available on the premises.)

When handling hazardous products, units should be equipped with suitable containment devices and systems should be put in place to eliminate the risk of cross-contamination.

2.4.7 Therapeutic risks and clinical consequences

When identifying the potential clinical consequences of a formulation failure or calculation error associated with an extemporaneously prepared medicine, it is important to review both the inherent properties of the drug and the patient's clinical condition as part of the risk assessment.

Any inaccuracy of dosing associated with medicines that have a narrow therapeutic index can lead to significant morbidity, whether due to underdosing leading to treatment failure or overdosing leading to toxicity. By contrast, any inaccuracy of dosing associated with drugs with a wide therapeutic index may have little or no impact on the therapy.

Patients with certain clinical conditions or from vulnerable patient groups may be at greater risk of morbidity than others and therefore it is important that the risk assessment takes into account the patient-specific circumstances rather than being solely a drug-based risk assessment.

Where there is significant risk of morbidity associated with a non-standard or complex formulation, all alternative options should be explored and extemporaneous preparation should be seen as a last resort.

2.4.8 Associated clinical risk factors

The majority of patients receiving extemporaneously prepared products, in particular oral liquid medicines, tend to be from vulnerable patient groups (e.g. neonates, children, stroke victims) who are either unaware of ill-effects associated with their treatment or who cannot communicate with their clinician. Coupled with this, extemporaneous preparations may not be routinely identified as high-risk therapies by pharmacists and therefore such treatments are not commonly given the level of scrutiny and close monitoring they require. Therefore when embarking on the use of an extemporaneously prepared product, the pharmacist should ensure that systems are in place to monitor the effectiveness of the therapy.

Pharmacists should regard patients receiving extemporaneous preparations as at increased risk and regularly review their condition to ensure the treatment is effective. Any issues should be documented and reported to the manufacturer (and MHRA if necessary for serious adverse events – see MHRA website for guidance) as part of an ongoing pharmacovigilance programme.

2.5 Managing the risks

The following checklists may provide a helpful summary guide to the risk management of patients requiring an extemporaneously prepared medicine.

2.5.1 Clinical risk reduction

- Identify extemporaneous preparations as high-risk therapy.
- Carry out a risk assessment.
- Consider alternative therapies.
- Review all available evidence to support the use of the preparation.
- Evaluate drug toxicity – consider therapeutic index.
- Monitor patient for clinical effect, toxicity and adverse drug reactions (ADRs).
- Document any problems and successful treatments for future reference.

2.5.2 Technical risk reduction

2.5.2.1 *Formulation*

- Use standard, validated formulae where possible (e.g. pharmacopoeia, expert report (industry generated), published papers).
- Evaluate data using first principles (in-house expert review by suitable qualified personnel, e.g. QC department).
- Gather information on or evidence of effective use from other units or pharmaceutical companies.
- Use information resources (e.g. Pharmaceutical Codex, Compounding Interest Group, NHS QA website – QAinfozone, Pharminfotech, Paddock Laboratories).
- If no formula is available, keep it simple using readily available, pharmaceutical-grade starting materials and standard vehicles.
- Restrict the shelf-life to limit degradation and spoilage (maximum of 28 days if preserved, 7 days if unpreserved).

2.5.2.2 *Preparation*

- Ensure extemporaneous dispensing facilities and practices comply with this guidance and are subject to systems of audit and self-inspection.
- Use QA-approved worksheets and procedures.
- Ensure facilities and equipment are appropriate and validated/calibrated.
- Ensure all operatives are appropriately trained.
- Use licensed or approved (e.g. QC-tested) starting materials.
- Perform COSHH assessment on both the starting materials and the preparation process.

2.5.2.3 *Risk matrix*

The risk matrix in Figure 2.1 may be helpful in risk evaluation.

Overall risk assessment	Low		Medium	High	
Risks to quality	Validated formula and supporting stability data available <ul style="list-style-type: none"> Published papers Pharmacopoeia Developed by licensed manufacturer <p>Rating: Low</p>	Formula available, but not validated. No supporting stability data <ul style="list-style-type: none"> Evaluation of formula and shelf-life from first principles by suitably experienced staff Experience of safe and effective use in NHS <p>Rating: Low</p>	Formula available, but not validated <ul style="list-style-type: none"> No supporting stability data or evaluation Experience of safe and effective use in NHS Reduced shelf-life (max 7 days) <p>Rating: Medium</p>	Formula available, but not validated <ul style="list-style-type: none"> No supporting stability data or evaluation No evidence of safe and effective use in NHS <p>Rating: High</p>	No formula available <p>Rating: High</p>
Risks to safety/efficacy	Low toxicity Short-term use <p>Rating: Low</p>	Wide therapeutic index Short-term use <p>Rating: Low</p>	Wide therapeutic index Maintenance therapy Vulnerable patient groups <p>Rating: Medium</p>	Narrow therapeutic index Short-term use Bioavailability could be significantly changed by crushing tablet <p>Rating: High</p>	Narrow therapeutic index Maintenance therapy Bioavailability could be significantly changed by crushing tablet <p>Rating: High</p>
H & S risks	Full supporting COSHH data Control measures in place <p>Rating: Low</p>			Inadequate supporting COSHH data No control measures in place No COSHH assessment carried out <p>Rating: High</p>	

Figure 2.1 Risk assessment matrix. Low risk: Prepare worksheet and make in accordance with local SOPs. Use licensed or QC approved starting materials only. Medium risk: Make for short-term use only and monitor patient for clinical effect and ADRs. Consider outsourcing to a 'Specials' unit or alternative therapy for long-term use. High risk: Consider all alternatives before making – only make as last resort. Monitor patient closely for clinical effect, toxic effects and ADRs.

2.6 References

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