Draft Guidance for Pharmacists on Extemporaneous Dispensing

Version 1

1. Introduction

The purpose of this guidance is to assist pharmacists in discharging their legal and professional obligations to patients in the area of extemporaneous dispensing. This guidance will help to assure the safe and appropriate preparation and supply of extemporaneously prepared medicinal products to patients where the supply of such products becomes necessary.

Extemporaneous preparation or manufacture refers to the process by which a pharmacist, using traditional compounding techniques, produces a medicinal product to meet the special needs of a patient, or group of patients, when no suitable authorised medicinal product is available.

The level of extemporaneous dispensing in Ireland appears to be increasing. This view is supported by the significant number of queries in relation to this, and related areas, that are being received on an on-going basis by the PSI. A number of legislative changes at a European level have also emphasised the need for a review of national guidance dealing with these products. Further information on these changes is provided in Appendix 1.

Unlike authorised (also called licenced) medicinal products, extemporaneously prepared medicinal products, by their very nature, have not undergone an evaluation of their quality, safety and efficacy by any competent authority such as the Health Products Regulatory Authority (HPRA) or the European Medicines Agency (EMA). Accordingly, the responsibility for assuring the quality and safety of these extemporaneously prepared products, with a view to the achievement of their therapeutic purpose, rests with the pharmacist under whose authority they are prepared. In the discharge of that responsibility, the added value which these products contribute must also be taken into account. For example the individual medical needs of the patient should be carefully considered and the possible availability on the market of an appropriate authorised alternative should be examined by the pharmacist.

In light of the lack of age-appropriate formulations, and the consequent need for extemporaneous dispensing to be undertaken for infants and children, it is essential to consider the issue of extemporaneous dispensing in the specific context of paediatric dispensing. Extemporaneous dispensing plays an important part in meeting paediatric patients' needs. However, as noted by the WHO steering group on paediatric medicines, *'Extemporaneous preparation poses a high risk to patient safety and is generally subject to low levels of quality assurance. Adherence to standards for extemporaneous dispensing is necessary to ensure safe preparation of good quality products. Standardising current products and formulae for which there is good quality efficacy and stability data and promoting this information is essential to improve current practice.'* Therefore, particularly careful consideration must be given in the assessment of the appropriateness of providing an extemporaneously prepared product to a child.

The pharmacist should always be satisfied that he or she has the necessary facilities and competence to undertake the extemporaneous dispensing, and is thereby in a position to supply a product of appropriate quality and safety. The pharmacist should be cognisant of the international good practice standards as set out by the *Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments*, published by the Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme (PIC/S) (available at http://www.picscheme.org/publication.php?id=8). This document provides detail on good practice standards for the preparation of sterile and non-sterile products in a pharmacy setting.

2. Legislative basis and Implications

The legal basis for the preparation of a medicinal product in a pharmacy, otherwise than in accordance with a manufacturer's authorisation from the HPRA, is contained in regulation 5(1) (a) of the Medicinal Products (Control of Manufacture) Regulations 2007. Similarly, the legal basis for the supply of a medicinal product, otherwise than in accordance with a marketing authorisation, is set out in Regulation 6(4) and Schedule 1 to the Medicinal Products (Control of Placing on the Market) Regulations 2007, including Article 3.2 of Directive 2001/83/EC[1].

Under this legislation, it is important to note that the supply of extemporaneously prepared medicinal products is permitted only in certain limited circumstances, as follows:

(i) in response to a *bona fide* unsolicited order of a practitioner (i.e. on foot of a prescription), where the medicinal product is for use by an individual patient or group of patients under the practitioner's direct responsibility and in order to fulfil the special needs of the patients concerned; or
(ii) in response to a request from a patient where the extemporaneously produced medicinal product is not subject to prescription-only control and is produced in the pharmacy in accordance with the specifications of the Pharmacopeia.

Extemporaneous preparation is not permitted in any other circumstances.

Whilst this would not exclude batch manufacture to maintain a limited stock of a particular product, caution should be exercised in view of the short shelf life of such products. Pharmacists must always be satisfied that any products they prepare are safe and fit for purpose both at the time of supply to the patient and throughout their expected shelf life. See also *Section 3.3.3 Expiry dates* below.

Where an extemporaneously prepared medicinal product is supplied under either of the circumstances as provided in the legislation above, the pharmacist must always make a written record as to its preparation. This should include the precautions taken to ensure that the product is of the character required and of the particular reasons that necessitated its preparation and supply.

In all cases, the pharmacist must be satisfied that the medicinal product concerned is not the subject of an advertisement and that no other authorised medicinal product of appropriate composition is available for use in the particular circumstances.

In this context, it is important to note that the decanting, relabelling and/or altering of the presentation of an authorised non-prescription medicinal product, or the combining of two or more non-prescription medicinal products is **not** permitted, other than in the circumstances outlined above.

[1] Directive 2001/83/EC on the Community Code relating to Medicinal Products for Human Use (O.J. No. L. 311, 28/11/2004, p. 67-128) (as amended).

3. Guidance

3.1 Key Responsibilities for Pharmacists

In light of the requirements as set out above and in consideration of the obligations of the pharmacist under their statutory Code of Conduct, the appropriateness of supplying an extemporaneously prepared medicinal product should always be carefully considered. The pharmacist must be satisfied that, having taken all the particular circumstances into account, the supply of any such preparation is necessary, is in the best interests of the patient and that it will add greater value to the care of the patient than would an authorised medicinal product in the particular circumstances. It is recognised that all health professionals involved, including the prescriber and the dispensing pharmacist, have, within their areas of responsibility, a duty of care to the patient receiving these pharmaceutical preparations. An appropriate quality assurance and risk assessment system must also be in place that takes into account the nature of the product requested, its ultimate quality and any risks that such product may present to the patient.

3.2 Decision Process (see also Decision Tree page 5)

In general, in the interests of patient safety, where at all possible, only medicinal products authorised for use in Ireland should be supplied. Where this is not possible, efforts should be made to source products that are authorised in another EEA country, or in a country where the standards of manufacture and control correspond with those in EEA countries (e.g. USA, Canada or Australia). These products are known as 'exempt' medicinal products where the term 'exempt' refers to products previously known as 'unauthorised' or 'unlicensed' medicinal products.

When deciding whether it is necessary and in the patient's best interest to extemporaneously prepare a medicine, the pharmacist should check if the prescribed medicinal product can be sourced through any of the following channels:

- From an authorised wholesaler or manufacturer of medicinal products in Ireland, including one of those specialising in the sourcing and supply of unauthorised (i.e. exempt) medicinal products;
- From an authorised wholesaler or manufacturer of medicinal products established in another EEA country, which can supply a product that has been authorised in that country, or if such a product is not available, an appropriately authorised alternative;
- From an authorised wholesaler or manufacturer of medicinal products established in another EEA country which can supply a product that has been authorised in a country where the standards of manufacture and control correspond with those in EEA countries. These supplies may only be procured through manufacturers or wholesalers, authorised within the EEA, that are permitted to make such importations;
- Consideration might also be given to the manipulation of the dosage form of an authorised medicinal product. In this context, it should be noted that the crushing or other manipulation of such authorised products (including the mixing with food or drink) constitutes an unauthorised use unless the procedure is provided for in the relevant Summary of Product Characteristics (SmPC).

Lists of, and information on, all Irish authorised manufacturers and wholesalers are available on the HPRA website (www.hpra.ie). The authorisation status of wholesalers and manufacturers based in other EU/EEA countries can be checked with the competent authority in the relevant country, e.g. the Medicines and Healthcare products Regulatory Agency (MHRA) in UK, etc. PSI *Guidelines on the Sourcing of Medicinal Products* provide further information on the sourcing and supply of 'exempt' medicinal products.

3.2.1 Specialist Compounding Facilities

If the prescribed product or an appropriate alternative is not available through any of the above channels, consideration may be given to the sourcing of an appropriate product, as an unauthorised medicinal product, from a specialist compounding facility which holds an appropriate manufacturer's authorisation from the HPRA for that purpose. Although these manufacturers hold a manufacturing licence it should be borne in mind that the products themselves have not been granted a marketing authorisation or undergone the relevant assessment required to obtain a marketing authorisation.

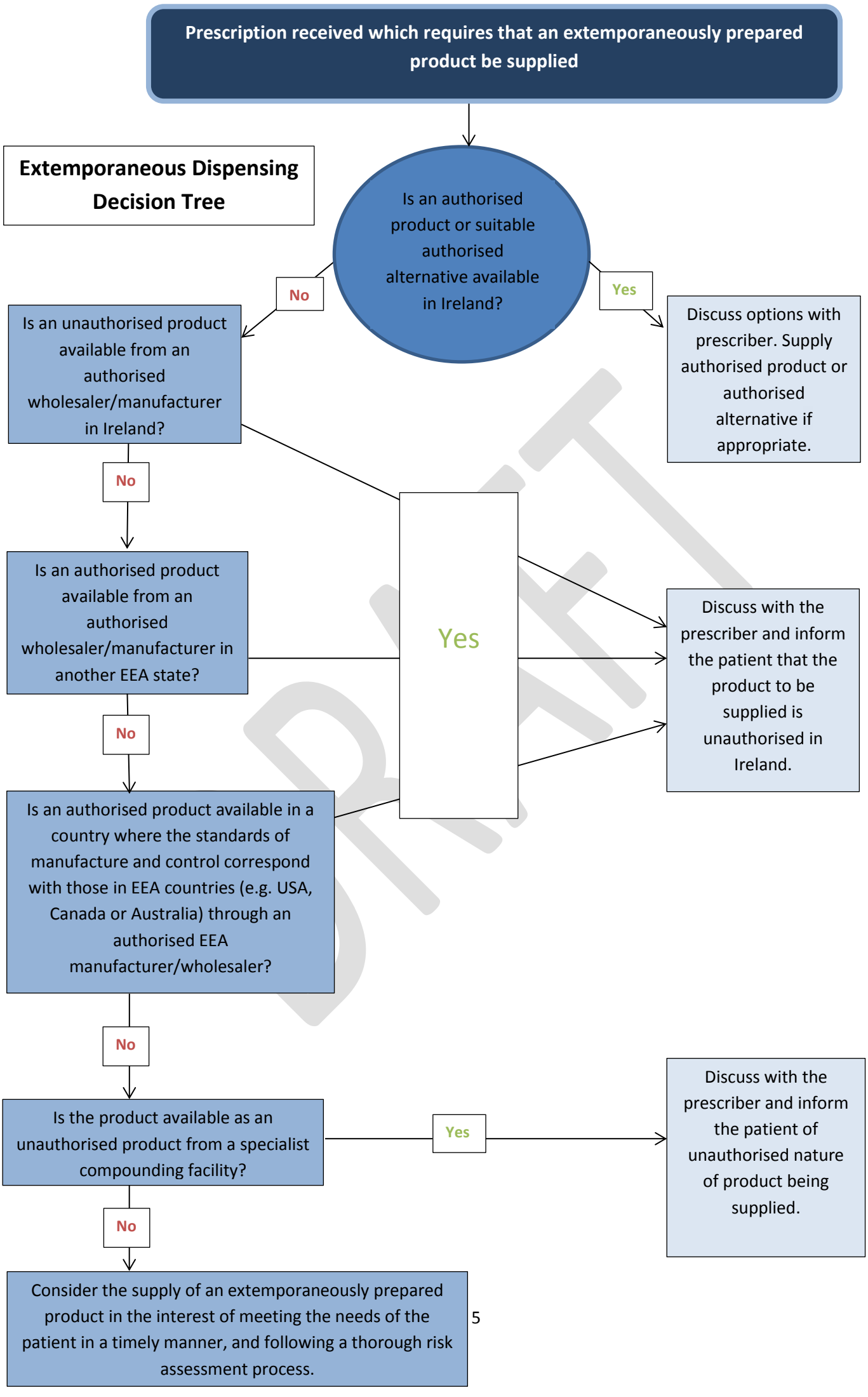
3.2.2 Extemporaneous Preparation

Pharmacists should only engage in extemporaneous preparation where all the routes of procurement described above have been exhausted or where it is not possible to obtain the patient's prescribed medicine via any of these routes without undue delay.

In light of the above requirements and in the interest of patient care and safety, a risk assessment should be carried out by the pharmacist prior to undertaking the dispensing of an extemporaneously prepared medicinal product. In doing this the pharmacist should consider if the preparation and supply of the product prescribed will add value to the care of the patient.

In the exercise of their professional judgement, the pharmacist may deem it necessary to review the clinical need for an extemporaneously prepared product in consultation with the prescriber. This should involve an assessment/review of the various alternatives to the supply of an extemporaneously prepared medicinal product. The prescriber should be made aware of any concerns that the pharmacist may have with regards to the supply of the product prescribed and the ethical and legal implications for all concerned. The necessity and importance of this dialogue is also emphasised in the European documents discussed in Appendix 1.

Pharmacists should also consider the urgency of the situation and endeavour to supply the prescribed product within an appropriate time-frame having regard to the needs of the patient. Where a more specialised product e.g. a sterile product, requiring specialist equipment and skills has been prescribed, it may be more appropriate for the pharmacist to obtain this product from a specialist compounding manufacturer or to refer the patient to a pharmacy specializing in the preparation of these products. Facilitating the needs of the patient in a safe and timely manner should be the primary concern of the pharmacist.


Prescription received which requires that an extemporaneously prepared product be supplied
Extemporaneous Dispensing Decision Tree
Is an authorised product or suitable authorised alternative available in Ireland?
No
Yes
Discuss options with prescriber. Supply authorised product or authorised alternative if appropriate.
Is an unauthorised product available from an authorised wholesaler/manufacturer in Ireland?
No
Is an authorised product available from an authorised wholesaler/manufacturer in another EEA state?
No
Is an authorised product available in a country where the standards of manufacture and control correspond with those in EEA countries (e.g. USA, Canada or Australia) through an authorised EEA manufacturer/wholesaler?
No
Is the product available as an unauthorised product from a specialist compounding facility?
Yes
Discuss with the prescriber and inform the patient of unauthorised nature of product being supplied.
No
Consider the supply of an extemporaneously prepared product in the interest of meeting the needs of the patient in a timely manner, and following a thorough risk assessment process.
Yes
Discuss with the prescriber and inform the patient that the product to be supplied is unauthorised in Ireland.

3.3 Risk Assessment

It is important in this context to consider the potential risks that are associated with the extemporaneous preparation of medicinal products in pharmacies. For example risks from:

- Calculation errors
- Formulation failures
- Microbial contamination
- Inappropriate starting materials
- Labelling errors
- Poor patient acceptability
- Health and safety issues

3.3.1 Calculations

Calculation errors pose the greatest risk of causing patient harm. Where at all possible, all calculations and measurements should be double checked by a second, appropriately trained, member of staff. This does not necessarily need to be another pharmacist. Explaining calculations and workings to another colleague can be enough to identify an error that may otherwise have been missed. Calculation errors can include:

- Conversion between units e.g. milligrams to micrograms.
- Confusion between a drug in its free base and its salt form.
- Administration errors, including 5-fold, 10-fold, 100-fold and 1,000-fold mistakes in measuring doses. Some of these mistakes have been attributed to inconsistent labelling approaches, for example, strengths expressed per millilitre or per 5 ml spoonful.
- Confusion surrounding decimal points.
- Errors whilst carrying out dilutions leading to 10-fold, 100-fold and 1,000-fold mistakes in a final formulation.
- A lack of knowledge and familiarity with traditional terminology used leading to serious error e.g. double strength chloroform water, single strength chloroform water and concentrated chloroform water.

A review of the proposed ingredients should form part of the risk assessment strategy as certain ingredients may pose greater risks to patients where a formulation is not appropriately prepared.

Risks to the pharmacist or other pharmacy staff, involved in preparing these products, through the handling of potentially hazardous materials should also be considered, particularly in the context of materials that may be carcinogenic or cause sensitisation, e.g. coal tar, chlorpromazine and salicylic acid. Gloves and protective clothing should always be used.

Such hazards should be reviewed by the pharmacist and all relevant information considered to ensure that the components used are appropriately stored, handled and used in a manner that will safeguard the health and safety of the patient, the public and all pharmacy staff.

3.3.2 Validity of the Formulation

Often previously used formulations are the primary resource used in extemporaneous dispensing; such records may not be current or appropriately referenced. Pharmacists must ensure that they are satisfied with the on-going validity of the formulation in use, from a quality, safety and efficacy perspective.

In this context, pharmacists should endeavour to use formulations in accordance with the specifications of the Pharmacopeia and/or make contact with the relevant specialist secondary care services for information on formulation e.g. Our Lady's Children's Hospital, Crumlin.

3.3.3 Expiry dates

In the interests of the patient and of the pharmacist, an appropriate expiry date should be included in the labelling of the product. The pharmacist should be satisfied that the expiry date applied is appropriately justified. Once the container is opened, it may be necessary to apply a clinically justified in-use expiry date.

3.4 Labelling

Extemporaneously produced medicinal products should be appropriately labelled in accordance with the requirements as set out in the Medicinal Products (Prescription and Control supply) Regulations 2003 (as amended) and in addition should meet all requirements as set out in the Council of Europe Resolution (see Appendix 1). Labels for extemporaneous products should be prepared before the product is compounded, to allow the product to be labelled as soon as it is prepared and avoid potential mislabelling or dispensing errors.

The labelling for extemporaneously dispensed products should include:

- the name of the patient,
- the name and address of the pharmacy,
- the date on which the product was dispensed,
- the name of the product, if applicable,
- the quantity of the product supplied,
- full qualitative composition and the quantity of the active substance,
- directions on the use of the product,
- batch number, if applicable,
- relevant precautionary warnings,
- the warning 'Keep out of the reach of children',
- route of administration e.g. 'For external use only',
- expiry date (including an in-use expiry date as appropriate) or information about limits for use,
- special storage conditions or handling precautions e.g. for certain liquid preparations 'Shake well before use'.

Correct labelling of the extemporaneously prepared product is essential in the interest of patient safety.

3.5 Record-keeping

A clear record in respect of each extemporaneously prepared product must be kept to ensure full traceability of the ingredients, formulae and method used, and the names of all pharmacist and staff members involved. The information to be recorded should be clearly documented in a written procedure. A recall procedure should be in place in case a defect or error is identified and the product has to be returned to the pharmacy.

Records should be maintained which clearly indicate, at a minimum:

- the patient's name,
- the patient's address and contact details,
- the name and address of the patient's doctor,
- other prescription details as applicable e.g. date, type of prescription,
- the date of preparation,
- the formulation used, and source e.g. pharmacopoeia formula,
- calculations and workings,
- preparation processes,
- each ingredient or material used, with batch number and expiry date where appropriate,
- the quantities used,
- the source of materials i.e. manufacturer and wholesaler,
- the storage conditions and expiry date of the finished product,
- the identity of the staff member who carried out the preparation process,
- the checking system, including the identity of the pharmacist under whose supervision this process was carried out.

A record sheet should be made for each individual preparation and a duplicate dispensing label affixed thereon. This record should be maintained for at least two years on the pharmacy premises and be available for inspection. This audit should facilitate a checking mechanism at each stage of the procedure.

3.6 Appropriate Facilities/ Equipment

Consideration should be given to the appropriateness of the premises and equipment of a pharmacy, and the staffing levels available at a given time, in the interest of the timely delivery of a safe and effective product to the patient.

All areas used in extemporaneous dispensing should be clean, orderly and well lit. All starting materials and finished product should be appropriately stored, to avoid mix-ups and/or cross contamination. Equipment used in these processes should be appropriately stored, handled, maintained and calibrated. Consideration should also be given to the type of container used to supply the product.

PSI Guidelines on the Premises and Equipment Requirements of a Retail Pharmacy Business provides further guidance on the requirements for extemporaneous dispensing.

3.7 Testing

The European legislation, as outlined in Appendix 1, applies significant requirements to products prepared in a pharmacy setting from the point of view of the testing of these products, in the process of quality control.

The European Pharmacopoeia monograph on Pharmaceutical Preparations specifies the necessity for tests to be applied to particular dosage forms, as described in their respective dosage form monographs, which are also applicable in the case of extemporaneously prepared products. Where it is not practical to carry out this testing (e.g. due to the batch size, urgency, etc.), other suitable methods should be implemented to ensure that the appropriate quality is achieved, in accordance with the risk assessment carried out. The requirements on testing in the European Pharmacopeia monograph deal with the appearance of products, identity and purity tests, uniformity and reference standards.

At a minimum, the starting materials and finished products should be examined visually before use or supply to a patient.

3.8 Education and Training

All staff involved in this service should be appropriately trained and the superintendent and supervising pharmacist must ensure that all staff involved maintain the necessary competence in this area. All training should be appropriately documented.

The superintendent pharmacist should be completely satisfied that the supervising and other pharmacist staff involved have the necessary competence and resources to undertake extemporaneous dispensing, and therefore are in a position to provide a product of appropriate quality and safety and which adds value to the care of the patient.

Pharmacists should self-assess their training and Continuing Professional Development (CPD) needs in the area of extemporaneous dispensing and monitor their competence from the perspective of their evolving practice requirements. Pharmacists should be mindful that they may need to refresh their knowledge, in the context that there may potentially be a considerable time lag between episodes of use of these skills.

3.9 Policies and Procedures

Adequate policies, procedures and quality assurance systems should be in place to ensure that products are consistently prepared to appropriate quality standards. Policies and procedures should be in place to ensure that all aspects of the provision of this service are appropriately managed and that policies and procedures are regularly reviewed to ensure compliance with best practice and particularly in response to any incident, error or near miss that may occur. All pharmacy staff should be familiar with these policies and should be trained in associated procedures, and re-trained in light of policy and procedure review or amendment. Appropriate records of these policies and procedures, their review, and staff training in this area should be maintained and kept in the pharmacy.

Appendix 1

Implications on extemporaneous dispensing should also be considered in light of the following:

(i) **The Council of Europe adoption of the Resolution CM/ResAP (2011)1, on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients**.

This considers the following important issues:

- the added value of pharmacy preparations and the responsibilities of healthcare professionals
- the preparation process (including a model procedure for risk assessment of the preparation based on a 'decision matrix')
- product dossiers (including quality control and stability testing)
- compliance with pharmacopoeial requirements
- labelling of extemporaneously prepared medicines
- communication and information for patients and their carers

The full document is available at - https://wcd.coe.int/ViewDoc.jsp?id=1734101&Site=CM

(ii) **The coming into force on the 1st April 2013, of the European Pharmacopoeia Monograph** entitled 'Pharmaceutical Preparations' (Monograph No: 2619 contained in Supplement 7.7 of the European Pharmacopoeia).

This applies to all pharmaceutical preparations including to the extent that it is practical, those medicinal products that are prepared extemporaneously.

In the case of unlicensed pharmaceutical preparations (which includes those that are prepared extemporaneously), it is recognised in the monograph that all health professionals involved, including the prescriber and the dispensing pharmacist, have, within their areas of responsibility, a duty of care to the patient receiving these pharmaceutical preparations.

Specific reference is made to the need for a suitable level of risk assessment to be undertaken whenever the supply of an unlicensed pharmaceutical preparation is contemplated. It is pointed out that the risk assessment is to identify:

- the importance of different parameters (e.g. quality of active substances, excipients and containers; design of the preparation process; extent and significance of testing; stability of the preparation); and
- the risk that the preparation may present the particular patient or patient group.

Compliance with the pharmacopoeial standards and requirements as set out in the monograph has been mandatory since the 1st April 2013.

(iii) The dependence of certain of the exemptions included in the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007) on the requirement that such "extemporaneously prepared" products be prepared in accordance with the prescriptions of a pharmacopoeia, which in this country is the European Pharmacopoeia.