

Quality, Safety and Efficacy in the 'Off-Label' Use of Medicines

Therése Eileen Kairuz^{*}, Derryn Gargiulo, Craig Bunt and Sanjay Garg

School of Pharmacy, University of Auckland, New Zealand

Abstract: Suitable dosage forms are not always available for specific patient populations and must be extemporaneously compounded. Extemporaneous preparation is the manipulation of drugs and excipients for a particular patient using traditional compounding techniques; these are referred to as 'off-label' and 'unlicensed' medicines. Off-label use can include altered doses, dosage forms or indications for use. Registered medicines are produced to internationally recognized standards of Good Manufacturing Practices. Within the pharmaceutical manufacturing industry, quality, safety and efficacy are enforced by regulatory legislations. In contrast, the responsibility for acceptable standards for the compounding of 'off-label' medicines falls on the prescriber, pharmacist or hospital nurse. Studies have been conducted by researchers from Australia and throughout Europe, highlighting the frequency of off-label use for paediatrics, with one study reporting that most extemporaneous preparations (29.6%) were for drugs required to treat metabolic diseases. Risks include compounding errors, adverse reactions to ingredients and excipients, and non-validated stability of the product. Sterile compounded products, including products for ophthalmic and palliative care, carry additional risks in these vulnerable patients.

This paper provides an overview of off-label medicines highlighting biopharmaceutical, quality, safety and efficacy issues important to medical and allied health professionals.

Keywords: Extemporaneous, compounding, off-label, unlicensed, quality assurance.

INTRODUCTION

Medicines are not always prescribed or administered within registered specifications in a particular country and would thus be used as 'unlicensed' or 'off-label' medicines. The term 'unlicensed' refers to medicines where the pharmaceutical manufacturer has not sought a marketing authorisation or product license for that medicine for a particular condition. It is sometimes necessary to use medicines to treat rare diseases such as congenital metabolism abnormalities and neonatal illnesses for which clinical trials have not been conducted, or for combinations of treatments undertaken during post-marketing surveillance [1]. 'Off-label' also includes the use of alternative routes of administration to that specified in the product license and administration of the medicine as a formulation not approved for use [2]. The two terms are often used interchangeably; however, the term 'off-label' will be used in this paper as it discusses issues surrounding the reformulation of medicines. The practice of using off-label medicines is provided for in the legislation in most countries, so that it is not illegal to prescribe, dispense or administer such medicines.

Off-label medicines are used for:

- Unspecified conditions and abnormalities
- Neonatal and paediatric illnesses without clinical trials
- Unapproved combinations of therapy
- Routes of administration other than those specified
- Dosage forms that have not been approved for that drug

Licensing of medicines was introduced in response to drug toxicity that affected both adults and children. In the United Kingdom (UK) the Medicines Act (1968), and in the United States of America (USA) the Kefauver-Harris amendment (1962), were legislated following drug toxicity in newborns (such as grey baby syndrome due to chloramphenicol) and drug toxicity in the developing foetus (such as phocomelia due to thalidomide) [3]. In the United States of America (USA), the regulation and control of pharmaceuticals is administered by the Food and Drug Administration (FDA). Approval of new drugs is based on the New Drug Application (NDA) and for generic drugs the Abbreviated New Drug Application (ANDA), which must be approved before U.S. commercialization [4]. In the UK the licensing process is administered by the Medicines and Healthcare products Regulatory Agency (formerly the Medicines Control Agency) on behalf of health ministers and a licensed medicine is granted Marketing Authorisation (formerly known as a Product License). The Marketing Authorisation includes clinical indications, dosage, age of patient, method of administration, precautions and other information. Pharmaceutical companies are permitted to promote products only for the uses and indications specified within the Marketing Authorisation. Formerly known as 'data sheets', the specifications are presented in the 'Summary of Product Characteristics' which are recognized sources of medicines information and which must be made available to doctors and other health professionals [5].

PREPARATION OF OFF-LABEL MEDICINES

Off-label medicines may be prepared from ingredients of pharmacopoeial standards or from chemicals without official standards which have not been sold for the commercial preparation of medicines [1]. The re-formulation of medicines into a suitable dosage form for a particular patient is referred to as 'extemporaneous compounding', which is

^{*}Address correspondence to this author at the School of Pharmacy, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand; Tel: +64-9-3737599, Ext. 84805; Fax: +64-9-367 7192; E-mail: t.kairuz@auckland.ac.nz

defined as 'the manipulation of various drugs and chemical ingredients with the use of traditional compounding techniques to produce suitable medications when no commercial forms are available' [1]. The practice involves mixing, measuring and making safe and aesthetically appealing pharmaceutical dosage forms [6] which are efficacious and meet quality standards.

AIM

This paper describes extemporaneous compounding of various dosage forms and discusses risks involved in compounding. It provides an overview of international perspectives and highlights issues of compounding in non-sterile, sterile and radiopharmaceuticals (Table 1).

Table 1. Contents

Extemporaneous Compounding	- a brief overview for clinicians - nasogastric administration - paediatric medicines
Good Manufacturing Practice (GMP)	- international perspectives
Risks of Off-Label Medicines	- compounding errors - adverse reactions - shelf-life of products - factors affecting stability
Pharmaceutical Considerations	- topical off-label products - oral off-label liquid preparations - solutions - suspensions
Aseptic Compounding	- palliative care - ophthalmology - quality assurance
Radiopharmaceuticals	- regulation
Recommendations	

The paper does not purport to provide an in-depth pharmaceutical review on each of these topics but rather aims to introduce the reader to an aspect of medicines that may not be considered in everyday clinical prescribing. Literature covers a variety of topics and online databases used included International Pharmaceutical Abstracts (IPA) and EMBASE. Approved internet websites were used to source regulatory documents. Criteria for selecting papers for review included research and review articles published in English. The following search terms were used:

- Extemporaneous
- Off-label
- Unlicensed medicine/s
- Pharmacist
- Compounding
- Paediatric medicines

EXTEMPORANEOUS COMPOUNDING: A BRIEF OVERVIEW FOR CLINICIANS

Extemporaneous compounding refers to the preparation of oral or topical products that does not require sterile equip-

ment and facilities. In 2002 the FDA issued the Compliance Policy Guide, Section 460.200, to provide guidance on compounding human drugs in a pharmacy, copies of which may be obtained from http://www.fda.gov/ora/compliance_ref/cpg/default.htm. Sterile preparations are discussed below in the section on aseptic compounding and includes the manufacture of eye-drops, bladder irrigation solutions, total parenteral nutrition products and cytotoxic compounds.

Pharmacists are the health professionals who are trained to perform extemporaneous compounding and it is a required competency of practice for registered pharmacists in many countries. In the 1940's and 50's pharmacists were trained to extemporaneously compound products such as oral liquids, solid dosage forms (Table 2), powders, creams and ointments. However, the rapid development of the pharmaceutical industry over the past 50 years has resulted in pharmacists primarily dispensing industrially produced medicines thereby decreasing the need for pharmacists to prepare dosage forms extemporaneously. The skill of the compounding pharmacist is required by various groups of patients, particularly those who cannot take solid dosage forms such as paediatric and elderly patients with swallowing difficulties, and those requiring naso-gastric administration.

Table 2. Selected Pharmaceutical Dosage Forms that Can be Extemporaneously Prepared

Liquid Oral Dosage Forms	
Solution	Homogenous mixture of two or more components, with the solute(s) dissolved in one or more solvents
Suspension	A disperse system in which one substance (the disperse phase) is distributed in particulate form throughout another (the continuous phase)
Emulsion	Two immiscible liquids, one of which is uniformly distributed throughout the other as fine droplets
Solid Oral Dosage Forms	
Capsule	Solid preparations intended for oral administration with a hard or soft gelatin shell, enclosing a medicament
Tablet	Solid preparations each containing a single dose of one or more active ingredient(s)

Compounding of Naso-Gastric Products

For delivery of extemporaneous products by naso-gastric tube, care must be taken during administration as there are perceived difficulties with adsorption of components to plastic tubing, aggregation of granules and tube blockage when the contents are administered as non-encapsulated granules in liquids [7]. It is important that solid dosage forms are suitable for re-formulation into liquids for administration at the low pH of the stomach. Enteric-coated tablets or capsule granules should not be crushed and re-formulated into liquids. For example, proton pump inhibitors (PPIs) are usually administered orally as capsules of enteric coated granules or tablets [7] but are often reformulated as suspensions in 8.4% sodium bicarbonate. The alkaline sodium bicarbonate is required to dissolve the enteric-coating of the granules which have been formulated to withstand the acidic

environment of the stomach so as to dissolve and release the active ingredient in the intestine. It has been reported that reformulation of omeprazole into an extemporaneous suspension results in reduced bioavailability and does not adequately inhibit intragastric acidity [7].

Compounding for Paediatric Patients

Paediatric patients have been described as 'therapeutic orphans' because they frequently do not have access to modern medicines licensed for use in their age groups. The range of oral formulations available for use in paediatric patients is limited and can differ between countries. For example, although the number of drugs licensed for children in New Zealand increased during the period 1998-2002, the number of commercially available paediatric dosage forms had decreased [8]. There are limited financial returns on children's medicines for the pharmaceutical industry and there are concerns about toxicity and ethical issues surrounding clinical trials in children [9]. Tablets and capsules are usually only available in 'adult strengths' [10], and accurate paediatric dosing is often not possible using solid dosage forms. Off-label use of medicines can provide alternative dosage forms facilitating paediatric compliance and titration of doses. Liver and kidney functions differ at various stages of paediatric development, requiring higher or lower doses in response-efficacy studies; children cannot be considered 'small adults' [11] and off-label medicines can be formulated to provide doses in easily-measured volumes. Off-label and unlicensed medicines are often used for paediatric patients and the European Agency for the Evaluation of Medicinal Products (EMA) proposed in 2003 that the Committee for Proprietary Medicinal Products (CPMP) consider preparing detailed guidance on formulations of choice for these young patients [12]. A recent study at a tertiary referral paediatric hospital in the UK reported that most extemporaneous preparations (29.6%) were for drugs required to treat metabolic diseases [13]. Other studies have been conducted in institutions in Britain [2], Australia [14, 15], Europe [16] and Germany [17], highlighting the frequency of off-label use.

GOOD MANUFACTURING PRACTICE (GMP)

The safety and effectiveness of a drug product depend on the potency, purity and quality of ingredients which in turn can be affected by how the drug is compounded. In the USA, a coalition of leading pharmacy related professional and regulatory organizations announced the creation of a voluntary accreditation programme for compounding. The Pharmacy Compounding Accreditation Board was established to help improve the quality of compounding; it will accredit pharmacy sites to undertake compounding and will also focus on quality assurance of processes [18]. The pharmacy compounding law (which is part of the Food and Drug Administration (FDA) Modernization Act of 1997) defines the limits of legitimate compounding, aiming to protect patients from unnecessary compounding. Quality control issues include the use of acceptable compounding ingredients and end-product testing. Quality assurance necessitates the use of standard operating procedures and suitably trained personnel [4].

Compounding procedures must be documented in sufficient detail to ensure that preparations can be replicated and that the history of each ingredient can be traced [19]. Documentation should include at least four sets of records: (1) compounding formulae and procedures, (2) a log of all compounded items, including batch records and sample batch labels, (3) equipment maintenance records, including checking of balances, refrigerators and freezers, and (4) a record of ingredients purchased, including certificates of purity for chemicals and medicines safety data sheets. In addition, the names of pharmacy compounders and the supervising pharmacist need to be documented.

Universities are working in collaboration with the pharmacy profession in various parts of the world to raise the standard of compounding. For example, the Florida College of Pharmacy (USA) provides an accredited Certificate Programme in compounding [20] and the University of Auckland in New Zealand offers a practical training course in aseptic compounding [21]. The preparation of (non-sterile) compounded medicines is a competence standard required for registration as a pharmacist in many countries, including Britain, South Africa, New Zealand and Australia. The Therapeutic Goods Administration (TGA) in Australia contracted Oceania Health Consulting to review compounding practices in that country and in their report in 2005 various concerns were raised. These included the wide range of preparations compounded by franchisee compounding pharmacies, the sourcing of raw materials, the apparent lack of material handling facilities and the use of certain ingredients which have been removed from the Australian Register of Therapeutic Goods on safety grounds [22]. Similar concerns have been raised in the USA while in other countries, such as Sweden, centralized compounding services are used to provide off-label or unlicensed medicines.

RISKS ASSOCIATED WITH OFF-LABEL MEDICINES

Risks in off-label compounding include using incorrect formulae and calculations, selecting incorrect ingredients, using incorrect quantities, and producing unstable products. The consequences can be fatal. In 2000 a baby died in England after receiving an off-label medicine that included chloroform; Chloroform Water Concentrate was incorrectly selected instead of Chloroform Water Double Strength, resulting in the fatality [23]. Compounded topical preparations can also cause fatalities. A 22-year student died after application of a topical gel containing 10% lidocaine, 10% tetracaine and an unknown amount of phenylephrine that had been extemporaneously compounded by a pharmacist; this had not been prepared from a prescription [24].

In addition to the systems errors that can occur in off-label medicines as described above, there are also adverse reactions to off-label medicines. They can be used for conditions or in patient populations for which clinical trials have not been conducted, and paediatric patients are particularly vulnerable [25]. Adverse reactions to off-label and unlicensed medicines for paediatrics were reported by Turner *et al.* [5] who found that the most severe reactions were to morphine and other opiates. It is also possible that patients of

all ages may experience adverse reactions not only to the drug itself, but to the chemical excipients that are used in compounded medicines.

Shelf-Life

There are implications for drug stability as well as altered pharmacokinetics in products prepared in an off-label manner. Stability is defined as 'the extent to which a medicine retains, within specifications and throughout the medicine's period of storage and use, the ability to possess the same stability as it did at the time of manufacture' [26]. The United States Pharmacopoeia (USP-NF) defines five types of stability, namely chemical, physical, microbiological, therapeutic and toxicological [27]. The range of factors that may affect the stability of a final product is listed in Table 3.

Table 3. Factors Affecting the Stability of a Product

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|---|
| <ul style="list-style-type: none"> • Physicochemical properties of each ingredient, such as particle size and pH • Chemical reactions that may occur in the formulation • Physical and environmental factors such as temperature, light, radiation and humidity • Contamination, especially with liquid formulations which often contain water • Packaging |
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PHARMACEUTICAL CONSIDERATIONS OF OFF-LABEL MEDICINES

Topical Off-Label Products

Topical preparations such as creams and ointments often need to be diluted to produce the prescribed strength [28] and incorporation of a second cream or ointment can result in chemical incompatibilities between ingredients and can reduce the stability of the product. For example, betamethasone valerate cream requires non-ionic cetamacrogol cream for dilution because the use of (anionic) aqueous cream results in inactivation of the (cationic) betamethasone valerate molecule over time. Other problems include reduction in preservative activity due to dilution.

Oral Off-Label Liquid Preparations

Most oral medicines are compounded as solutions or suspensions. Additional ingredients known as excipients are required to ensure acceptable, stable products. The following section provides an overview of various excipients including their usefulness and potential risk.

Solutions

A solution is a homogenous one-phase system consisting of two or more components with the solute dispersed as small molecules or ions in the solvent. Drugs that are not highly soluble in water tend to be problematic, requiring alteration in their formulation to increase solubility without altering drug stability [29]. Co-solvents such as propylene glycol (propane 1, 2-diol), glycerol and ethanol are often used to improve solubility. Propylene glycol is a polyalcohol that is generally considered a stable solvent with low systemic toxicity. It is metabolised *via* normal systemic

pathways and is partially excreted unchanged by the kidney; it is also partially oxidized to lactic acid and pyruvic acid which enter the glycolic pathway. In neonates the half-life of propylene glycol is approximately 16.9 hours compared to 5 hours in adults [29] and should be used with caution in products for children under the age of three years. Risk factors for undesirable effects from propylene glycol include accumulation of a large total dose of a medicine containing a high proportion of propylene glycol. Renal insufficiency in susceptible patients, and the additive effects of propylene glycol when it is used as an excipient in multiple medicines prescribed to a single patient, can compound the problem.

Glycerol (propane-1,2,3-triol) is a similar compound to propylene glycol but with a sweeter taste; it has higher viscosity and does not have the same potential for increasing the solubility of poorly water-soluble drugs. Consumption of large amounts of glycerol can cause diarrhoea and severe dehydration, and circulatory overload may result from the withdrawal of water from extra-vascular spaces [30].

Alcohol (ethanol) is also used to enhance solubility of poorly water-soluble drugs and ethanol 90% is the strength that is usually used for compounding. The amount used as an excipient can cause toxic effects in patients who have an idiosyncratic reaction to alcohol, and in patients using drugs that demonstrate a disulfiram-like effect. Some off-label formulations contain unacceptably high quantities of ethanol for paediatric patients, such as Phenobarbitone Elixir BP and Phenobarbitone Elixir BPC, which contain over 30% ethanol [31]. Glycerol and sorbitol have been suggested as alternative excipients for the off-label compounding of phenobarbitone sodium. Alcohol-free preparations are now recommended for neonates and children.

The compounding of off-label preparations sometimes includes the use of parenteral solutions which are reformulated for oral use. There are factors besides commercial availability which must be considered when evaluating whether an injectable solution is suitable for oral use. Drugs in solution in an injectable form may be absorbed more rapidly compared to drug release from a solid dosage form and the total amount of drug absorbed will be variable. The injectable form of drugs which are chemically degraded by gastric acid are unsuitable for oral administration and will have poor bioavailability. Injections may contain excipients which are undesirable for oral use and the cost of reformulating an injection may be prohibitive.

Suspensions

Grinding tablets and dispersing them in suitable vehicles is a method frequently used to compound off-label medicines. Excipients such as antimicrobial preservatives and suspending agents are required to ensure product stability. Flavourants and colourants may be added to enhance compliance or for identification. These formulations can be complex and can lead to inaccurate dosing due to the formation of hard sediments that are not readily dispersed on shaking. Soluble tablet excipients released into a reformulated liquid product may alter the pH of the preparation resulting in precipitation, instability and degradation. Compared to solutions, in which dose uniformity is not an issue, suspensions may require more than one suspending agent to ensure dose uniformity. Taste is an important issue

with oral liquid medicines. Solid dosage forms are often coated or encapsulated to mask the bitter taste of drugs. On converting to a liquid form, the bitter taste can become very pronounced. The use of sweetening and/or flavouring agents is often the best option for reformulated products.

ASEPTIC COMPOUNDING

Aseptic compounding guidelines have been published to assist with the implementation of USP Chapter <797>, Pharmaceutical Compounding: Sterile Preparations [32]. Practice recommendations for sterile compounding were issued by various organizations during the 1990s and the first official enforceable guidelines took effect on January 1, 2004, when USP published USP Chapter <797>. Across the ocean the European Commission (EC) published the EC Guide to Good Manufacturing Practice- Revision to Annex 1 – Manufacture of Sterile Medicinal Products in 2003 [33] which emphasises the need for quality assurance in order to minimize risks, although it does not lay down detailed methods for determining microbial and particulate cleanliness. The following section gives the reader a brief overview of aseptic compounding and the need for quality assurance for safe patient outcomes of treatment.

The need for quality assurance in aseptic compounding was highlighted in a report published in 1976 in the UK [34]. The report was commissioned after several incidents of patient mortality resulted from poor compounding processes of aseptic products. One of the recommendations of the report was that all aseptic extemporaneous compounding be conducted by pharmacists in a centralised aseptic production unit. In 2000 in the USA the FDA identified procedures of compounding that met the requirements for being difficult to compound [35]. Foremost of these procedures was aseptic compounding.

Aseptic extemporaneous compounding is the manipulation of sterile ingredients to achieve an end-product which remains in the sterile state [36]. The commercial preparation of sterile products utilizes methods such as high temperatures, high pressure, ethylene oxide or gamma radiation. These methods are not suitable for certain ingredients, such as antibiotics, due to their chemical nature or instability under extreme conditions. Parenteral products are used frequently in hospital environments when immediate pharmacological effect is necessary such as in emergency situations or when other routes of administration are not appropriate. Types of parenteral products range from prefilled syringes, to the infusion of therapies *via* intravenous bags including nutrition [37]. Two areas of extemporaneous compounding that frequently require aseptic techniques are palliative care and ophthalmology.

Palliative Care

Patients in the terminal stages of their illness often have an escalation of symptoms which necessitate the use of off-license medications. Symptoms such as neurogenic pain, dyspnoea, agitation, dysphagia and cough need to be controlled but the patient is often unable to take oral medications. The subcutaneous route is used to facilitate the delivery of medications; however few medications are licensed for this approach. Difficult symptom control is given as the reason for unlicensed use of medications in a study pub-

lished in Palliative Medicine [38], with just over a third prescribed *via* the subcutaneous route. Similar findings were reported by Todd and Davis (1999) [39]. The use of off-label compounded products in palliative care patients is further complicated by the issue of informed consent. Patients who are prescribed off-label products that are aseptically compounded or administered *via* an off-label parenteral route should be informed about the risks involved [40]. However, this informed consent may not be possible in the patients' terminal phase due to cognitive impairment, increasing anxiety levels and the possibility of refusal of beneficial treatment [41]. It is also unreasonable to subject the patients' family to complex information during this vulnerable period.

Ophthalmology

Ophthalmologists prescribe products for a number of conditions which require the use of unlicensed medications or strengths [42]. Chemical burns are treated with ascorbic acid eye drops, severe infective keratitis is treated with a combination of fortified aminoglycoside and cephalosporin eye drops and severe dry eye syndrome (keratoconjunctivitis) is treated with acetylcysteine eye drops. An off-label route used in ophthalmology is intra-vitreous injection, in which a small amount (0.1ml) of medication is injected into the vitreous humor of the eye. These products are compounded by pharmacists in an aseptic production unit as they are either not available commercially or, if a product is available, the concentration may not be appropriate.

Quality Assurance

Patient injuries and deaths over the last twenty years have highlighted the need for quality in extemporaneously compounded aseptic medicines [43]. Many of these cases resulted from inadequate quality control measures. A 1995 survey of USA hospital aseptic production units reported that few hospital pharmacies were equipped with adequately controlled compounding environments nor were essential quality control checks being carried out [44]. The survey was repeated in 2002 which highlighted the fact that not much had changed in the interim [45].

For products that are aseptically compounded there are five possible sources of contamination [46]:

- contamination by touch
- surface contamination of components
- airborne contamination
- contamination during storage
- contamination during administration.

Human error or operator technique influences all of the above risk factors and has been implicated as the major variable for medication error in aseptic compounding [47]. Therefore, the quality, safety and efficacy of aseptically compounded products rely heavily on the aseptic manipulative skills of the operator.

COMPOUNDING OF RADIOPHARMACEUTICALS

The compounding of radiopharmaceuticals in many countries may or may not be covered by codes of GMP or regulated by agencies that have responsibility for pharmaceuticals. For example, in New Zealand the National Radia-

tion Laboratory has responsibility for radiopharmaceuticals while the New Zealand 'Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods' does not address such products. In the United States radiopharmacy safety is overseen by the Nuclear Regulatory Commission (NRC) regulations 10CFR 20.1101 and 35.20. While sites qualifying as a nuclear pharmacy can be exempted from manufacturing regulations [48], the Radioactive Drug Research Committee (RDRC) Program of the FDA does regulate some aspects of radiopharmaceuticals of which further information may be obtained from <http://www.fda.gov/cder/regulatory/RDRC/>. FDA guidance addresses developing medical imaging drug and biological products in terms of safety, clinical indications and interpretation of clinical studies. Proposals for a review of the regulation of positron emission tomography (PET) molecular imaging probes have been presented to address the differences between radioactive diagnostic probes and therapeutic drugs [48]. The FDA has recently drafted the 'Guidance for PET Drug Products - Current Good Manufacturing Practice' (CGMP) for comment purposes only [49].

RECOMMENDATIONS

When licensed medicines are unavailable in a specific country, medical professionals may need to exert 'political' pressure on governments to source products elsewhere, especially for chronic, critically ill or for very young patients. In the hospital sector, pharmacists must ensure that good manufacturing principles are implemented and that raw materials of adequate quality and appropriate formulae are sourced for off-label medicines. In the community, especially where compounding facilities are often inadequate and off-label products may be seldom prescribed, prescribers and pharmacists must ensure that any off-label products that they compound meet current quality assurance standards. In many countries compounding is being recognised as a field of speciality and it may be safer and more cost-effective, for the patient and the pharmacist, to send such prescriptions to a central, accredited compounding facility.

CONCLUSION

Extemporaneous compounding is a skill that is required of pharmacists to provide medicines for patients that are safe, effective and of acceptable quality, and includes the compounding of sterile and non-sterile products as well as radiopharmaceuticals. Quality control and quality assurance are vital components of extemporaneous compounding. Although there are inherent risks in compounding all of these products, the medicine produced may be the only manner in which the patient will receive the required drug in a suitable dosage form.

ACKNOWLEDGEMENTS

M. Dogra, for assistance with the manuscript. P. Gargiulo (B. Pharm, M. Sc) for guidance on the final version of the manuscript.

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