

# **EVALUATION OF EXTEMPORANEOUS COMPOUNDING IN TERTIARY HOSPITAL PHARMACY IN THE POLOKWANE MUNICIPALITY – A PILOT STUDY**

**by**

**Euphenia Mathebule Masupye**

Submitted in partial fulfilment of the requirements for the degree of Masters in Medical Sciences in the Discipline of Pharmaceutical Sciences of the School of Health Sciences at the University of KwaZulu-Natal



**UNIVERSITY OF<sup>TM</sup>  
KWAZULU-NATAL**

---

**INYUVESI  
YAKWAZULU-NATALI**

**Supervisor:** Prof F Suleman

**Co-Supervisor:** Prof T Govender

**Date submitted:** June 2015

*“Your work is going to fill a large part of your life, and the only way to be truly satisfied is to do what you believe is great work. And the only way to do great work is to love what you do. If you haven't found it yet, keep looking. Don't settle. As with all matters of the heart, you'll know when you find it”.*

**Steve Jobs**

## **DECLARATION – PLAGIARISM**

In fulfilment of the requirements for the degree of Masters of Medical Sciences in the Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa, I, Euphenia Mathebule Masupye, declare that:

- i.** The research reported in this dissertation, except where referenced, is my original work.
- ii.** The dissertation has not been submitted for any degree or examination to any other university.
- iii.** This dissertation does not contain other persons' text, tables, data, graphs, or other information, unless specifically acknowledged as being sourced from other persons.
- iv.** The dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:
  - a)** their words have been re-written but the general information attributed to them has been referenced;
  - b)** where their exact words have been used, their writing has been placed inside quotation marks and referenced.

Signed:-----

Date: -----

Student number: 208523748

## **ABSTRACT**

### **Background:**

Some medicines are available in doses that are not suitable for a specific population group and therefore manipulation of the existing medication is undertaken in order to obtain the required concentration of that medication. The groups affected by this include paediatrics, adults who are unable to swallow (such as, geriatric patients); those who are fed using naso-gastric tubes; and the terminally ill. Studies on the practices, frequency and extent of extemporaneous compounding have been undertaken in other countries such as New Zealand, Australia, United Kingdom, United States of America, the Netherlands and Mexico. No published data currently exists for South Africa. Extemporaneous compounding studies are essential for improving the care of patients particularly in South Africa with its complex and unique challenges.

### **Aim:**

The aim of this pilot study was to explore the extemporaneous compounding practices in a South African public sector setting.

### **Methods:**

This was a pilot study using a cross-sectional descriptive design. Purposive sampling was used to sample both the hospitals and the pharmacists. A self-administered close-ended and open-ended questionnaire was designed to collect information from willing pharmacists for exploring the compounding practice processes. All the batch records from April 2008 to March 2009 were purposively sampled for frequency and extent of compounding to obtain information on dosage form, medicine classification and route of administration. The descriptive analysis was done using Statistics Package for Social Sciences (SPSS Version 20, 2011).

### **Results:**

Fifty-nine questionnaires were distributed to tertiary hospital pharmacy personnel, of which 25 were returned (a 42.37% response rate). The main findings were that almost all of the pharmacists (96%) reported receiving compounding skills training and 60% of the respondents confirmed that the expiry date was personally developed. There was no proof of

records being kept on the regular calibration of electronic weighing balances (76%) and maintenance (72%) despite the fact that documentation for compounding comprising of manufacturing batch records (80%), as well as compounding formula and procedures (72%) are mostly kept. The maintenance of electronic weighing balances was in the most instances, not carried out (64%). A logbook of all compounded medicines was commonly not kept (64%). A key finding was that there was limited training in aseptic technique (3%), which, if not applied correctly, could result in contamination of compounded products.

About 691 batch records were reviewed for the study period. The most compounded medicines were dermatologicals (46.60%), with, creams and ointments totalling 33.0% and 13.60%, respectively. The most compounded product was Betamethasone cream (27.9%) .

### **Conclusion:**

The findings suggest that there seem to be insufficient skills within the tertiary hospital pharmacy staff for small scale compounding. Documentation on equipment calibration and maintenance was not available in most cases. The findings of this pilot study highlight the need for further such studies across South Africa to identify and improve extemporaneous compounding training and practice in the country.

## **DEDICATION**

This work is dedicated to:

My mom: Mmaneng Mokhwazo, and the sacred memory of my father, Kubyana Mokhwazo

My children: Boitumelo, Thapelo and Koketso Masupye

My grandchildren: Keaobaka, Lentumetse, Tshimologo and Bokamoso

My son-in-law: Sammy Phalane

My sisters: Diarona, Mpho and Koba

My brother: Ntebaleng Mokhwazo

My sister-in-law: Nonhle Mokhwazo

## ACKNOWLEDGEMENTS

To Jehovah the Most High God for sound mind, strength and enabling grace to complete this work.

I am indebted to the following people without whom this study wouldn't have been possible:

Supervisor: Professor Fatima Suleman for guiding and supervising my work.

Co-supervisor: Professor Thirumala Govender for her patience, tenacity, gentle persuasion and guidance in co-supervising my work from inception to the very end.

Mr GT Mahlatsi for the support and encouragement at the very beginning of this work.

Professor RN Malema for her mentorship and motivation when I was on the verge of giving up and for her valuable encouragement from conception to completion of this study.

Professor N Nyazema for his support and keen interest in my study.

Mr MN Netshidzivhani and Mrs R Olwagan for their assistance with my statistical analysis.

The Limpopo Provincial Department of Health and Social Development for granting me permission to conduct the study in the province.

The pharmacy managers at different hospitals in the Polokwane Municipality and their teams for their cooperation and willingness to provide information and space during the data collection sessions.

The University of Limpopo for financial assistance.

University of Limpopo Women's Academic Solidarity Association (ULWASA) for encouraging and supporting contemporary Postgraduate women (Students and Staff) to become successful scholars and researchers in their discipline of study.

The University of KwaZulu-Natal Ethics Committee for approving my application to conduct this study (HSS/0984/2009).



## Contents

DECLARATION .....	ii
ABSTRACT.....	iii
DEDICATION .....	v
ACKNOWLEDGEMENTS.....	vi
LIST OF ABBREVIATIONS .....	x
LIST OF TABLES .....	xi
CHAPTER ONE: INTRODUCTION.....	1
1.1 Introduction.....	1
1.2 Background to the study .....	1
1.3 Aim and objectives of the study.....	5
1.4 Significance of the study.....	5
1.5 Novelty of the study.....	5
1.6 Overview of the dissertation .....	6
CHAPTER TWO: LITERATURE REVIEW .....	7
2.1 Introduction.....	7
2.2 History of extemporaneous compounding and standard definition .....	7
2.2.1 Terminology and concepts of extemporaneous compounding.....	9
2.3 Importance and application of extemporaneous compounding .....	10
2.4 Risks and concerns associated with extemporaneous compounding.....	11
2.4.1 Concerns and limitation of extemporaneous compounding.....	14
2.5 Quality of extemporaneously prepared medicines.....	15
2.6 Standard of pharmacy personnel skills and practice in extemporaneous compounding .....	17
2.7 Global studies on extemporaneous compounding .....	20
2.7.1 Mexico .....	21
2.7.2 United Kingdom.....	21
2.7.3 Australia .....	22
2.7.4 New Zealand .....	22
2.7.5 United States of America.....	22
2.8 Conclusion .....	23
CHAPTER THREE: SUBMITTED MANUSCRIPT.....	24
3.1 Introduction.....	24
3.2 Submitted manuscript .....	25
CHAPTER FOUR: CONCLUSIONS AND RECOMMENDATIONS .....	41
4.1 Introduction.....	41

4.2 Conclusions.....	41
4.3 Limitations of the study .....	42
4.4 Recommendations for future work .....	42
4.5 General Conclusion.....	43
4.6 Declaration of interest.....	43
REFERENCES .....	44
LIST OF ANNEXURES .....	53
ANNEXURE 1: Confirmation for submission of Manuscript.....	53
ANNEXURE 2: Ethics Committee letter of approval .....	55
ANNEXURE 3: Letter of approval to conduct the study in the province .....	56
ANNEXURE 4: Letter of approval to conduct the study at the hospital.....	57
ANNEXURE 5: Data collection tool for pharmacists .....	58
ANNEXURE 6: Data collection sheet for the compounded medicines .....	64
ANNEXURE 7: Consent form for the pharmacists.....	65
ANNEXURE 8: Map of the province (Mapsofworld.com).....	67

## LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
ARVs	Antiretrovirals
ASHP	The American Society of Health-System Pharmacists
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPP	Good Pharmacy Practice
HIV	Human Immune Deficiency Virus
JCAHO	Joint Commission on Accreditation of Healthcare Organization
MCC	Medicines Control Council
SADC	Southern African Development Community
SAPC	South African Pharmacy Council
SPSS	Statistics Package for Social Sciences
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

## LIST OF TABLES

NUMBER	TITLE	PAGE
<b>CHAPTER 2 – Literature Review</b>		
<b>Table 2.1</b>	Terminology commonly used to describe extemporaneous compounding	9
<b>Table 2.2</b>	Global compounding studies	20
<b>CHAPTER 3- Submitted Manuscript</b>		
<b>Table 1</b>	Demographic profile as percentages of the total sample	31
<b>Table 2</b>	Compounding skills training areas	32
<b>Table 3</b>	Documentation of Compounding in the hospital	33
<b>Table 4</b>	Resources used for obtaining formulations in hospital pharmacy	33
<b>Table 5</b>	Establishing expiry dates	35

## **CHAPTER ONE: INTRODUCTION**

### **1.1 Introduction**

This chapter provides a background to the need for the study and the aim and objectives of the study. It also describes the novelty and significance of the research that was undertaken.

### **1.2 Background to the study**

The lack of appropriate dosage forms, dose or strength for specific groups of patients is widespread and has resulted in the need for extemporaneous compounding worldwide (Brion et al., 2003; Calvalho et al., 2008; Giam et al., 2011). In other cases, sensitivity/allergy to the excipients and preservatives, shortage, discontinuation of medicines, special combination or orphan medicines contribute to the need for compounding (Sellers and Utian, 2012). Examples of the groups or individual patients catered for by extemporaneous compounding are paediatrics, geriatrics or those adults who have difficulty swallowing solid dosage forms and those for whom medication is administered in a liquid form through naso-gastric tubes due to poor swallowing reflexes necessitating extemporaneous compounding (Standing and Tuleu, 2005).

Extemporaneous compounding is, therefore, usually prepared from commercially available or existing solid dosage forms (Brion et al., 2003; Haywood and Glass, 2007; Spark, 2014), in a dose or dosage form (Haywood and Glass, 2007) not suitable for the above-mentioned groups with the aim of providing drug formulations that are effective and well-tolerated by patients (Nahata and Allen, 2008), or may entail the crushing of tablets or dispersing the capsule contents into a suitable liquid dosage form which may require the inclusion of excipients such as flavourants (Haywood and Glass, 2007). These mask the bitter taste. A suspending agent, which is required to facilitate and distribute the crushed tablets into the solution for dose uniformity, is also added so that the tablet excipients that are usually insoluble in water are suspended. Colorants, preservatives and viscosity enhancers are other excipients that are added in the suspension for compounding a liquid dosage form.

Giam and McLachlan (2008) define extemporaneous compounding as “extemporaneous preparation, mixing, packaging or labelling of a medicine as the result of a practitioner’s prescription of medicine in order to meet an individual patient’s need”. In this study extemporaneous preparation is defined as products made or compounded in a pharmacy on a small scale to meet patients’ specific requirements within all age groups, or a tailored therapy for a specific patient (Brion et al., 2003; Gross, 2005; Schultz, 2007). The practice of extemporaneous compounding for this study involved a small scale manufacture of preparations, using raw materials or commercially available dosage forms to reformulate a suitable dosage form at an appropriate strength for a specific patient of any age group. The practice of extemporaneous compounding is necessary to ensure that paediatrics and adult patients receive appropriate formulations of medicines to meet their specific requirements (Brion et al., 2003). Extemporaneous compounding, therefore, has diverse applications and is critical in patient health care and optimizing treatment outcomes.

Whilst it is widely used, numerous concerns and challenges pertain to this compounding practice. One of the concerns is lack of standardized ways of preparing different compounded preparations for different patients. In other words, there is limited stability data for numerous preparations that are frequently subjected to extemporaneous compounding (Nahata et al., 2000). Since the stability of such preparations is unknown, this may lead to formulations being given a short or long expiry date. Globally, the pharmaceutical services do not prescribe standard protocols for extemporaneous preparations and, as such, there are high risks with extemporaneous compounding. In a 2006 survey conducted by the Food and Drug Administration (Food and Drug Administration, 2006), some of the challenges were the improperly compounded, adulterated medicines having the potential to cause significant harm to patients. This survey emphasized that without strict observance of Good Manufacturing Practice (GMP) guidelines, it is possible to have miscalculations of the respective quantities of each ingredient and this could be problematic, especially where the system and processes are not tightly regulated. The survey indicated that there were inadequate standards related to compounding, with no auditing against those standards and these had posed a high risk of harm to patients’ health. Another concern was the global lack of pharmacists in most hospitals, and this puts pressure on those who were employed due to the additional workload. Another study pointed to poor compounding techniques by untrained compounding personnel, leading to mishaps, such as the anti-cancer drug case in

2001 in Kansas City where 158 chemotherapy doses for 34 patients were diluted to a lower concentration. This affected 98 000 prescriptions given to 4200 patients whose lives were at risk of wrongful death which involved 400 physicians (Oceania Health Consulting, 2005). In the same year in California, one pharmacist was linked to three deaths from meningitis as a result of bacterial contamination of a compounded Betamethasone injection that was administered to 38 patients (Oceania Health Consulting, 2005). In Atlanta in 2002, four patients were hospitalized, with two falling into a coma, after swallowing a compounded Thyroxine hormone which was 1000 times more concentrated than the prescribed strength (Oceania Health Consulting, 2005). These tragedies raised concerns regarding extemporaneous compounding practices and their limitations. The global lack of documentation and standardized formulations poses a high risk to patients as there may be variations in manufacturing methods used and also the excipients used may differ greatly and their effect on the stability and quality of the compounded medicine cannot be guaranteed. The stability testing guidelines for instance, may also help in producing medicines of stable, efficacious and acceptable quality.

Various countries such as New Zealand (Kairuz et al., 2007a), Australia (Feldschuh, 2008), the United Kingdom (Stewart et al., 2007), the United States of America (Treadway et al., 2007), the Netherlands (Giam and McLachlan, 2008) and Mexico (Flores-Perez et al., 2008) have undertaken studies to determine the skills of staff compounding medicines, as well as the frequency and extent of extemporaneous compounding practice. Compounding did decline from 10-15% to 5% in the Netherlands in the 1990s (Buurman et al, 2003). The compounding practice is also confirmed by the retrospective survey conducted in 2007 by Kairuz et al. in the two New Zealand hospitals where the findings revealed the most frequently compounded preparations to be Solatol for neonates and infants, Labetolol, Clonidine for infants and children, and Diazoxide for infants. About 0.5% of all prescriptions were extemporaneously compounded in England in 2001, including off-label medicines (Donnelly et al., 2008). Buurman et al. (2003) in their study reported a frequency of 3.4% for compounded prescriptions dispensed by the Dutch community pharmacy. Dermatological products were found to be the most frequently compounded medicines.

Since compounding has shown to be occurring, it is the responsibility of pharmacists in the hospital settings to assure the quality of all compounded preparations (Agharowa et al., 2013). This is largely due to their professional obligations and training, enabling them to undertake extemporaneous compounding by ensuring that all formulations are in accordance to acceptable compounding standards (Lowley and Jackson, 2008). Compounding skill is a required competency practice for registered pharmacists in many countries; hence, quality assurance (QA) necessitates the use of suitably trained personnel to produce a safe and quality product (Kairuz et al., 2007a). Compounding practice is generally based on the following standards: 1) the hospital pharmacy personnel or the type of staff who are involved in compounding, 2) training methods, 3) documentation, 4) compounding formulation and the source, 5) how expiry date is determined, 6) what equipment is used and 7) the reasons for compounding. Clear Standard Operating Procedures (SOPs) should be in place for major items of compounding and equipment. The safety and quality of extemporaneously compounded preparations should be ensured by compounding a product with an expected potency and its characteristics maintained to the time of expiry. Safety risks may, therefore, be minimized through skill, training and knowledge on QA procedures.

Whilst aspects of extemporaneous compounding have been studied and reported for the countries above, such as the frequency and extent of the practice, formulation optimization or development of regulatory policies, there are no such published studies to date reported from South Africa on the subject matter, except those published studies in South Africa by de Villiers (2005) and Tetty-Amlalo (2005) at the Universities of Potchefstroom and Rhodes respectively. Their studies were on extemporaneous compounding which were, however, focused on the optimization of compounded formulations and not on establishing the status of extemporaneous compounding. Labuschagne et al. (2005) presented a poster at the 26th Annual Conference of the Academy of Pharmaceutical Sciences of South Africa on the stability of the formulation of novel drug dosage forms of antiretroviral drugs. Aspden et al. (2011) presented a poster to determine the methods of extemporaneous compounding teaching methods in five countries: South Africa, New Zealand, Canada, Australia and the United Kingdom. In Jamaica, Harries et al. (2011) presented a poster on optimization and the compounding practice in the same country. In South Africa there are complex health challenges, various groups requiring age-appropriate medicines compounded extemporaneously for improving health care. By documenting such practices, locally



developed and locally relevant Standard Operating Procedures and formulations can be developed.

### **1.3 Aim and objectives of the study**

#### ***1.3.1 Aim of study***

The aim of this pilot study was to explore the extemporaneous compounding practices in a South African public sector setting.

In order to achieve the above aim, the objectives of this pilot study were:

1. to assess the skills set and capacity of the staff compounding medicines in the tertiary hospital pharmacy in the Polokwane Municipality;
2. to determine the most common dosage form and product being compounded in the tertiary hospital pharmacy in the Polokwane Municipality.

### **1.4 Significance of the study**

The findings of the study will contribute to the following:

- Identification of a potential need for the development of guidelines and Standard Operating Procedures (SOPs) for extemporaneous compounding in hospitals.
- Identification of areas of skills development in pharmacy personnel involved in extemporaneous compounding.
- Identification of a potential gap in the education of pharmacists at an undergraduate level.
- The need for further research in this area.

### **1.5 Novelty of the study**

Extemporaneous compounding studies in several countries such as New Zealand, Australia and the Netherlands have been reported to date (Kairuz et al., 2007b). However, in South Africa with its complex health challenges and various groups requiring specially compounded medicines, no such studies have been published.

## **1.6 Overview of the dissertation**

This section of the report seeks to highlight the contents of each chapter.

### **CHAPTER ONE: INTRODUCTION**

The chapter gives an orientation to the study, which includes the background to the need for the study, the aims and objectives and the significance of the study.

### **CHAPTER TWO: LITERATURE REVIEW**

This chapter contains a detailed literature review on the theoretical aspects of extemporaneous compounding and includes an identification of such studies reported globally.

### **CHAPTER THREE: SUBMITTED MANUSCRIPT**

The chapter presents the results of the study in the form of a submitted article on determining the skills of the pharmacists in preparing compounded preparations as well as the frequency and extent of compounding in order to assess compounding standards.

### **CHAPTER FOUR: CONCLUSIONS AND FUTURE STUDIES**

In this chapter, conclusions are generated from the main findings of the study and their significance is highlighted. Limitations of the study and recommendations to improve or maintain compounding practice are presented.

## **CHAPTER TWO: LITERATURE REVIEW**

### **2.1 Introduction**

This chapter presents an appraisal of the literature on extemporaneous compounding. It focuses on its applications and current concerns. The chapter also discusses various studies undertaken globally to identify the frequency and the extent of extemporaneously compounded medicines as well as the standards thereof.

Most commercial medicines are unavailable in dosage forms that are suitable for specific groups of patients (Nahata et al., 2000). As such, extemporaneous compounding is necessary to provide health care to population groups of patients such as geriatrics and other adults who are not able to swallow solid dosage forms such as tablets and capsules due to swallowing difficulties (Argoff and Kopecky, 2014). Another group benefitting from this practice are paediatric patients (Kairuz et al., 2007a; Aquilina, 2013). Regulatory bodies set the standards for regulating the manufactured medicines (Oceania Health Consulting, 2005) but no such standards exist for extemporaneously compounded medicines (Lowey and Jackson, 2008). The lack of quality control measures increase the risks associated with compounding by putting patients at risk (McCague et al., 2012) such as contamination in medicines; more so, as there are no quality control tests done to assure the safety and quality of those medicines (Gudeman et al., 2013). Pharmacists are health care professionals who receive formal training in compounding medications and are licensed to dispense (Eley and Birnie, 2006). This literature review reveals the importance of the abilities and skills possessed by the pharmacists to minimise risks to patients. The keywords that were used as search terms were: extemporaneous compounding; compounding; and compounding practice, and the search engines that were incorporated into the review were: Google; Google Scholar; Web of Knowledge; Science Direct; Pubmed up until March 2015. It was hoped that by using Google and Google Scholar any unpublished studies from South Africa would be captured.

### **2.2 History of extemporaneous compounding and standard definition**

Extemporaneous compounding practice dates back to the ancient biblical times where priests or medicine men administered to the sick portions of syrups as they carried out the

religious rituals (Cox Pharmacy Wellness Centre, 2005). In the 9th century, the first compounding evidence was recorded in Baghdad and the science subsequently spread to Europe (Cox Pharmacy Wellness Centre, 2005). According to Riley (2004), “compounding has been a part of pharmacy practice for over 4000 years when the pharmacist applied the art of selecting, extracting and preparing medicines from vegetable, animal and mineral-substances in an acquirement that must have been almost as ancient as man himself on earth”.

According to Riley (2004), “when the first United States Pharmacopoeia was published in 1820 in the United States, pharmacists still compounded most prescriptions. In the 1920s a “broad knowledge” of compounding was still necessary for 80% of prescriptions dispensed”. In the 1930s and 1940s, 60% of the medications were compounded. There was a decline in the 1950s and 1960s due to the advent of commercial manufacturing of medicines (Riley, 2004). Another steady decline was observed in the 1980s due to the emergence of the compounding companies such as Paddock Labs and Spectrum (Riley, 2004). Extemporaneous compounding has been the traditional role of the pharmacist which declined with the availability of manufactured medicines (Chowdhury et al., 2012). While pharmacists no longer compound individualised prescriptions to the extent they did in the 1930s and 1940s, they still compound commercially available medicines (Kolling and McPherson, 2013). For example, a pharmacist may be requested to prepare an oral liquid solution for an infant from crushed tablets or powder, in a suitable base, in the absence of an appropriate dosage form or strength for children, and these are often referred to as extemporaneously prepared medicines and the practice occurs internationally (Patel et al., 2011; Arghahowa et al., 2013).

The practice of extemporaneous compounding, therefore, describes “small scale manufacturing which entails the manipulation by the pharmacists of various medicines (active) and chemical ingredients using traditional compounding techniques to produce suitable medicines (dosage form) when the commercial forms that are available are inadequate or cannot be used as formulated” (Brion et al., 2003; Winfield, 2004; Nahata and Allen, 2008;). These extemporaneously compounded preparations are prepared in a pharmacy in response to an immediate request by a prescriber, in limited quantities for an individual patient (Aquilina, 2013), through a medical prescription. In this study

extemporaneous preparations are defined as products made or compounded in a pharmacy on a small scale to meet specific patients' requirements of all age groups.

### ***2.2.1 Terminology and concepts of extemporaneous compounding***

In this section terminology and concepts of extemporaneous compounding are presented.

In the United States, the Food and Drug Administration (FDA) regards traditional pharmacy compounding as "the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized medical needs of an individual patient" (FDA, 2006). Schultz (2007) defines extemporaneous medicines as products made or compounded in a pharmacy on a small scale to meet a specific patient's specific requirements (all age groups) or a tailored therapy for a specific patient. In this study, the practice of extemporaneous compounding involved a small scale of manufacture of preparations, using raw materials or commercially available dosage forms to reformulate a suitable dosage form at an appropriate strength for a specific patient of any age group with a specific condition.

Table 2.1 below shows the definition of extemporaneous compounding terms that are used interchangeably.

**Table 2.1: Terminology commonly used to describe extemporaneous compounding**

<b>Term</b>	<b>Description</b>	<b>Reference</b>
Extemporaneous compounding	"The reformulation of medicines into a suitable dosage form for a particular patient".	Kairuz et al., 2007a
Compounding	"The preparation, mixing, packaging or labeling of a medicine as the result of a practitioner's prescription medicine" in order to meet an individual patient's need".	COX Pharmacy Wellness Centre, 2005

Term	Description	Reference
Extemporaneous preparation	“Preparations prepared from commercially available solid dosage forms with the aim of providing access to, among others, age-appropriate medicine formulations that are effective and well-tolerated by patients”.	Haywood and Glass, 2007  Nahata and Allen, 2008

### 2.3 Importance and application of extemporaneous compounding

Extemporaneous compounding practice has a long history (Chowdhury et al., 2012). According to the WHO, the rational use of medicines, which, in New Zealand and Australia has evolved into the Quality Use of Medicines (QUM), demands that appropriate medicines of quality, safety and efficacy be accessible to all patients at the right time, cost, suitable dose and dosage form (Kairuz et al., 2007a). While the different federal approved medicines meet the therapeutic needs of most patients (Sellers and Utian, 2012), there are circumstances in which extemporaneously compounding plays a vital part in medical care (Treadway et al., 2007). The compounding practice improves the health of different patient population groups who are unable to swallow solid dosage forms. Since “oral drug delivery using solid dosage forms such as tablets and capsules is the most common and popular route of administration to deliver medications into the body” (Manrique et al., 2013; Lau et al., 2015), some patient population groups might be deprived of access to the potential therapeutic benefits of medicines (Manrique et al., 2013).

Therefore, extemporaneous compounding caters for the availability of medicines to geriatrics and other adults who are unable to swallow solid dosage forms due to poor or compromised swallowing reflexes (Argoff and Kopecky, 2014). Another patient population group benefitting from this practice of extemporaneous compounding is paediatrics (Argoff and Kopecky, 2014) as most solid dosage forms are usually available in adult strength and accurate paediatric dosing is often not possible using tablets and capsules (Kairuz et al.,

2007a). Another diverse application of extemporaneous compounding is in dermatological or palliative care (Gross, 2005), where a combination of topical dermatological medicines are custom-made in a limited quantity to meet the clinical needs of an individual patient (Aquilina, 2013). Extemporaneous compounding practice is necessary as part of the health system to ensure availability of a prescribed drug at the right time at an affordable price to special-need and specific patient populations (Milner and Bruss, 2008), who lack access to approved medicines and formulations (Sosnik et al., 2012).

Although compounded medicines are prepared in limited quantities for individual patients, according to Aquilina (2013), bulk compounding is a common practice in the National Health Service in countries like England, and such a practice violates both the pharmacy and the medicine acts for human use (Gross, 2005). There are again those community pharmacies in the United Kingdom (UK) which primarily dispenses ‘specials’ as observed by Calvalho and Tuleu (2008). Another common compounding practice in European countries such as Portugal, Spain and Germany is compounding made for stock in anticipation of a prescription (Gross, 2005). Locally, there are no published records showing the occurrence of such practices.

## **2.4 Risks and concerns associated with extemporaneous compounding**

Although the compounding practice shows global prevalence, extemporaneous compounding activities carried out in pharmacies today bears the highest risk and poor quality has often proven to be the evidence to support the occurrence of risks (Lowley and Jacson, 2008). In other words, extemporaneous compounded preparations generally “lack studies to document stability, bioavailability, pharmacokinetics, pharmacodynamics, efficacy and safety” (Sellers and Utian, 2012), “leading to increased toxicity, e.g. crushing an extended-release solid dosage form may lead to dose dumping; undesirable side effects and decreased efficacy. Furthermore, crushing an enteric coated tablet may result in destruction of the active ingredient in the acidic environment of the stomach and unpalatability, resulting in poor patient compliance” (Sellers and Utian, 2012).

There is a lack in previous studies to document stability, bioavailability, pharmacokinetics, pharmacodynamics, efficacy and tolerability (Patel et al., 2011), and the safety of compounded medicines may be compromised. There is also elevated risk in newborn infants

because they are more likely to be predisposed to adverse drug reactions due to their physiological immaturity (WHO, 2007). In previously studies by Glass and Haywood (2006), looking into considerations when preparing a liquid dosage form from the commercially available medicine, the findings were that formulations may also contain preservatives; an excipient considered to be largely inert in adults could lead to life threatening toxicity in paediatrics when multiple doses of medications with the same preservative are employed. Children are not small adults hence their physiological development and bioavailability of medicines is different from that of adults. Therefore the direct extrapolation of the clinical data to predict the medicine absorption, distribution, metabolism and elimination cannot be done accurately from adult clinical data (Standing and Tuleu, 2005; Barnes, 2008). Such inaccurate dosing can put children's lives at risk either by underdosing or overdosing which can expose paediatric patients to toxic effects of the medicines (Barnes, 2008).

Furthermore, depending on their age many children are unable to swallow a solid whole tablet or capsule, even when given training on how to do so (Standing and Tuleu, 2005). There is again a problem in dosing accuracy as dosing is often based on body weight. This was observed by the first comprehensive summary reviewed by Glass and Haywood (2006) of tablets often cut into smaller segments in the ward to obtain appropriately sized dosage units for children. Their observation was that "those segments cannot be cut with great accuracy of dose. This is contradictory to the findings of Brion and colleagues (2003) who identified it as an alternative way to prepare medication for the paediatric population. Standing and Tuleu (2005) cited an audit at Great Ormond Street (GOSH) in London (UK), one of the seven specialist pediatric hospitals in England, where it was found that "manipulations such as tablet cutting, tablet crushing and opening of capsules was necessary to administer 26% of oral doses given to in-patients, although the data was not published". According to Standing and Tuleu (2005), splitting tablets leads to dose inaccuracy, and crushing the tablets can affect absorption and cause therapeutic failure.

In some instances, the risks associated with compounding may be fatal to the point of causing deaths. Large scale compounding may adversely affect many patients due to errors which might occur in the process (Gudeman et al., 2013). For example, in the most recent study conducted by Staes et al. (2013), the findings in the fungal meningitis outbreak caused by medicines compounded by the New England Compounding Center indicated that there



were “11 infectious outbreaks from contaminated compounded preparations involving 207 case-patients with 17 deaths between 2000 and prior 2012” (Staes et al., 2013). Staes and colleagues reported “the 2012 meningitis outbreak increases totals of death cases to almost 5-fold”. Their findings further determined that “the state health agencies identified 490 case-patients with serious fungal infections, including meningitis, stroke or other central nervous system-related infection and joint infections, where 34 case-patients died and the outbreak involved 19 states, and that the Compounding Centre estimated that approximately 14 000 patients received injections from 3 lots of methylprednisole”.

Other examples include the “peppermint water case”, cited by Lowey and Jackson (2008), where “the use of concentrated chloroform-water led to the death of a child. This case highlighted the dangers of potent ingredients and calculation errors, particularly where the strength of one or more ingredient is stated in a historical or non-standard fashion”. Similar reports have originated from the US, with the death of a child from a super potent imipramine liquid, and a five-year-old child who received a 1000-fold overdose of clonidine (Glass and Haywood, 2006; Lowey and Jackson, 2008). “It has been estimated that more than 40% of doses given in paediatric hospitals require compounding to prepare a suitable dosage form since crushing a tablet and/or sprinkling the contents of a capsule over food or mixing it in a drink may lead to errors in preparation or delivery of doses” (Patent google, 2011). The formulation of paediatric medicines therefore demands more than simply cutting a tablet into half, or suspending the capsule’s contents in water to get the correct dose for administration to this group.

Other concerns associated with extemporaneous compounding practice are that there is very little clinical data and evidence-based information on optimal dosages, frequency of dosing, efficacy and safety in pediatrics when new drugs reach the market. While the World Health Organization and other statutory bodies demand that an appropriate medicine be made available in an appropriate dosage form and the correct quantity be dispensed at the right time, and that it be taken in the right dose for the length of a prescribed treatment period, the lack of evidence for medicines for some groups of patients is widespread. Such lack has sparked the initiation of this extemporaneous compounding practice worldwide (Brion et al., 2003; Giam et al., 2012). To ensure the appropriate preparation dosage form and dosing regimen the skills and judgement of both the pharmacist and the physician become critical.

These risks raise concerns regarding extemporaneous compounding practices and their limitations which are outlined below (Oceania Health Consulting, 2005).

#### ***2.4.1 Concerns and limitation of extemporaneous compounding***

##### ***a) Limited validated stability data***

There are no reports published or documented in any form of stability of extemporaneous preparations. The stability data is lacking for numerous medicines that are frequently subjected to extemporaneous compounding. Pharmacists are performing a broad range of extemporaneous compounding activities from oral solutions to powders as highlighted by Crawford and Dombrowski (2008) in their survey. It is apparent that there is a need for documented stability and other information on extemporaneous medicine formulations (Kairuz et al., 2007a).

##### ***b) Short expiry date***

The stability of extemporaneous preparations may be unknown, leading to these formulations being given an untested shelf-life. Further, environmental conditions differ in countries, thus necessitating stability studies congruent with realistic storage conditions of the extemporaneous preparation.

##### ***c) Shortage of pharmacists***

Compounding is time consuming. Due to the global shortage of pharmacists in the country, (Buurman et al., 2003), the current pharmacists find themselves pressurized by heavy workloads, making compounding a challenge in most hospitals. In 2004 and 2005, Butler conducted a pilot Dispensing Service Research Project in 29 pharmacies in South Africa. According to Butler (2006) regarding the workload of pharmacists in the activities of dispensing, these are the differences in timelines: it takes 8.7 minutes for a pharmacist to dispense complex and uncomplicated medicines (complex counselling with all dispensing steps included) compared to 18 minutes 45 seconds per complicated (compounded) medicine item, the longest time being the interpretation evaluation phase which is the first phase of dispensing.

##### ***d) Untrained personnel***

Possession of a qualification as a pharmacist or pharmacist's assistant does not necessarily imply adequate skills to carry out all functions efficiently and independently. Additional in-service training may be required in specific areas (FDA, 2006). There is a potential for poor

compounding techniques, leading to cross-contamination and human error with untrained personnel (FDA, 2006).

***e) Quality assurance procedures***

The essence of quality assurance is to provide proof of what is claimed to be taking place or supposed to be taking place in terms of the processes in the extemporaneous compounding practice. In South Africa compounding is regulated by the South African Guidelines of Good Manufacturing Practice. These guidelines specify minimum standards required to maintain the quality of medicines and to ensure patients' safety. They are standard requirements considered by the Medicines Control Council's (MCC) quality control procedures to ensure medicines' quality, while pharmacists are governed by the South African Pharmacy Council (SAPC). The MCC, however, is not in a position to enforce compliance by compounding hospitals and pharmacies. The SAPC does not have a large inspectorate workforce to assess the quality of extemporaneously compounded preparations made on a small scale at the hospital pharmacies based on the specified standard of quality as a regulatory body. In the US, the United States Pharmacopeia (USP) and the American Society of Health System Pharmacists (ASHP) have developed guidelines on compounding procedures for the pharmacist in an attempt to help raise the standards of compounding and prevent the risk of patient harm. There are no such guidelines and sets of standards in South Africa. Milne and Bruss (2008) suggested that internationally harmonized guidelines for extemporaneous compounding to supplement formulation needs are required.

## **2.5 Quality of extemporaneously prepared medicines**

Medicines are subject to regulation to provide acceptable quality, safety and efficacy of the product. Medicines are registered and approved for intended usage by regulatory bodies in different countries, guided by the Good Manufacturing Practices (GMP) guidelines. "These guidelines are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements" (Canadian GMP guidelines, 2009). Important players in the current environment on ensuring the safety, quality and efficacy of medicines are the regulatory bodies in different countries. The quality of compounded preparations is ensured by adherence to the standards outlined in the guidelines. To ensure this, a good quality assurance system incorporating GMP should be in place.

The World Health Organization has recommended a special role for pharmacists in the quality assurance and safe and effective administration of drugs. This practice by pharmacists is governed by the South African Guidelines for Good Manufacturing Practice (GMP) which specifies the minimum standards required to maintain the quality of the product and ensure the safety of patients. These guidelines include a number of standards that should be nationally and internationally compliant and comparable with those of the agencies like the World Health Organization (WHO) and the Food and Drug Association (FDA).

Compounding practices, which individually influence the quality of medicines, are based on the standards in the Pharmaceutical Inspection Co-operation Scheme (PICS) guidelines, the European Pharmacopoeia which is used as an official regulation for the extemporaneous preparations and the South African regulatory body, the MCC. The standards are discussed below using the following variables:

(a) **Good documentation** “constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of information for drug reaction for an example. Specifications, compounding formulae and instructions, procedures, and records must be free from errors and available in writing. Clear Standard Operating Procedures (SOPs) should be in place for major items of compounding and equipment. The documents should be legible ” (USP, 2014).

(b) **Premises and equipment** must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, buildup of dust or dirt and, in general, any adverse effect on the quality of products” (USP, 2014).

(c) **Personnel** – “The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of GMP

that affect them and receive initial and continuing training, including hygiene instructions relevant to their needs” (USP, 2014).

The WHO is the directing and coordinating authority for health within the United Nations system (Oceania Health Consulting, 2005). Its responsibility is to provide for leadership on global health matters, shaping the health research matters, setting the health norms and standards, providing technical support to countries and monitoring and assessing health trends, while the International Conference Harmonization (ICH) is seen as the element that facilitates the commercial relationship between the Southern African Development Community (SADC) countries, and to ensure that the entire region benefits from the rapid availability of medicines which are safe, efficacious and of quality. The ICH includes the United States of America, Japan and the European countries (Oceania Health Consulting, 2005). The well regulated countries are Canada, Australia and the Nordic region.

According to the European Agency for the Evaluation of Medicinal Products (EMA, 2002) meeting, there are no common European standards or guidance for extemporaneous preparations in contrast to those manufactured medicines that have to comply with GMP requirements. There is, therefore, a possibility of having different standards and it may be that not all of them would yield a safe, good quality and efficacious product. Extemporaneous compounding is guided by GMP guidelines, including standards for the equipment utilized, the staff involved in the process, the storage of raw materials and the finished product and specifications for the premises.

## **2.6 Standard of pharmacy personnel skills and practice in extemporaneous compounding**

Although extemporaneous compounding has inevitably remained the domain of the pharmacist, some evidence reveals that other professionals, especially medical specialists such as naturopaths and herbalists (Feldschuh, 2008), also do it, even when the modern scientific technologies have produced new chemical entities. Allen (2012) insist that pharmacists possess knowledge and skills that are unique and not duplicated by any other profession.

The goal of this study was to look at the level of competency of the compounding staff in the compounding practice in an attempt to provide access to safe and quality

extemporaneously prepared preparations to specific groups of patients. As such, pharmacists are often faced with the prospect of preparing new prescribed dosage forms not commercially available and tailored to the patient's therapeutic needs. Again, pharmacists in the hospital settings are responsible for assuring the quality of all compounded preparations, largely due to their professional obligation and training enabling them to perform extemporaneous compounding (Nunn, 2003). Compounding skill is a required competency for practice for registered pharmacists in many countries (Kairuz et al., 2007b).

Whether or not South African hospital pharmacies have adequate equipment and storage facilities for the raw materials used for compounding extemporaneous products is a topic for another study. What is very clear though is that documentation of activities involving this practice need to be kept and updated throughout the process (Schultz, 2007). The principle of good documentation is that it is an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, manufacturing formulae and instructions, procedures and records must be free from errors and available in writing. The legibility of documents is of great importance (Steinborn, 2004). Hence, Pharmacy Compounding was issued to establish guidelines for personnel and training, product classification and storage, beyond-use dating, equipment storage and maintenance and environmental control for quality (USP, 2014). These guidelines are in accordance with the 2014 USP Chapter 795, which aims to assure that compounding pharmacies use methods of quality assurance for all compounded products produced. The importance of these quality assurance methods is to help maintain the quality of the product at every stage of compounding to the point of dispensing, which again minimises the chances of adverse medicine events. This is so that the products maintain quality after leaving the pharmacy and so that adverse medicine events are prevented (Flores-Perez et al., 2008).

According to the guidelines of the 2014 USP Chapter 795, all pharmacists are to comply with the record keeping requirements for their individual states. Compounding documents are kept as standard guides of information to allow the next compounder to reproduce the same prescribed preparation. The compounding record lists the excipients and the person responsible for the compounding activity and the formulation record serves as the consistent source document for preparing the preparation. The formulation record lists the name, strength and dosage form of the preparation. It further includes the preparation ingredients

with their quantities, the equipment used and the method for mixing. The expiry date of the preparation is also included. These records' retention period is the same as that required for any prescription, which is normally three years. According to Kairuz et al. (2007b), "the skill to compound non-sterile products is one of the seven competencies required of entry-level pharmacists for registration with the New Zealand Pharmacy Council". The need for extemporaneous compounding skills has been questioned in other countries, as it is argued that the skill is not often required in modern pharmacy settings (Kairuz et al., 2007a). Compounding risks can therefore be minimized through pharmacists' skills for producing quality preparations, and by training with knowledge on quality assurance procedures.

Possession of a qualification as a pharmacist or pharmacist's assistant does not confer ability to carry out all functions. The level of the compounding skills and expertise, together with compliance to quality assurance procedures possessed by the pharmacists, were studied in Texas by Treadway et al. (2007) and the findings were that pharmacists did not receive training. However, policies and procedures on extemporaneous compounding were adhered to. The sources for compounding formulation were from published literature and no stability testing were done on the finished medicine produced.

In the US, the pharmacy compounding law which is part of the Food and Drug Administration (FDA) Medicines Act of 1968 and Modernization Act of 1997 respectively define the limits of legitimate compounding. These guidelines specify minimum standards required to maintain the quality and to ensure the safety of patients. According to a report by Oceania Health Consulting (2005), Australia has standards and guidelines that could ensure the quality of compounded preparations meeting very basic requirements, but the application of those standards seem to be a "hit-and-miss process" to compounding pharmacies, with no certainty from a national perspective. Standardized USP guidelines and the external enforcement of those guidelines by regulatory bodies such as the Joint Commission on Accreditation of Healthcare Organization (JCAHO) have the potential to be a significant step forward in further improvement of pharmacy compounding practices (Oceania Health Consulting, 2005). In this review of the need for further regulation of compounded preparations, the consultants indicated the lack of enthusiasm in setting compounded preparations quantity limits. The other reason is that compounded preparations are required to be produced to an appropriate standard, and quantity cut-off does not ensure that quality. Large scale compounding is done in anticipation of the need for the dosage

form. Batch production, where a medicine is compounded for one patient specifically, is a concern to the Therapeutic Goods Administration as it has increased in other areas.

However, it is still important that those who are compounding locally do so with compliance to GMP requirements in mind. The legislation in most countries, including Europe, Australia and the United States, allows this practice (Giam and McLachlan, 2008). In all these countries the GMP needs to be adhered to for all compounded products as they are not regulated as compared to the commercially available products. This is done so as to ensure that the product compounded is safe, of good quality and, once in use, efficacious.

## 2.7 Global studies on extemporaneous compounding

The studies done globally that have been reported from various studies are summarised and presented below in Table 2.2:

**Table 2.2: Global compounding studies**

Aspects of extemporaneous compounding studied	Sector of pharmacy	Country	Reference
Practice	Hospital	France and Canada	Prot-Labarthe et al., 2007
Frequency	Hospital Emergency Care	Arizona	Phan et al., 2010
Frequency (drug consumption patterns)	Hospital	Mexico	Florez-Perez, 2008
Frequency	Hospital	Malaysia	Lee et al., 2012
Extent	Hospital pharmacy	New Zealand	Kairuz et al., 2007a
Education (practices of pharmacies)	Institutional and hospital pharmacies	United States of America,	Treadway et al., 2007



Education (methods of extemporaneous preparation)	Hospital pharmacy	United Kingdom	Brion et al., 2003
Formulation optimization	Hospital and community pharmacy	Australia	Glass and Haywood, 2006
Development of regulatory policies	Hospital and community pharmacy	Germany	Barnes, 2008  Breitkreutz, 2008

Table 2.2 indicates that studies encompassing frequency, extent, compounding education, development of regulatory policies and formulation optimizations related to extemporaneous compounding have been undertaken in other countries. It can be clearly seen (Table 2.2) that no such published study to date has been reported within South Africa on this subject. This is specifically needed within the South African setting due to the complex health challenges within the country and the clear existence of disease conditions and group of patients requiring extemporaneous compounded preparations.

The main findings from some of the studies above are discussed hereunder:

### ***2.7.1 Mexico***

Flores-Perez et al. (2008) surveyed Mexico to determine the pattern of medicine consumption at the National Institute of Pediatrics from 2001 to 2006. They also developed a list of medications for which there is no adequate pediatric formulation. It was found that furosemide, phenobarbital, omeprazole, midazolam, prednisone and captopril were the most frequently prescribed medicine for which no paediatric formulation is available. This could imply that this reflects increased cases of metabolic syndrome in children necessitating the use of these medicines which were normally only used predominantly in adults.

### ***2.7.2 United Kingdom***

Each year 26% of children in the UK receive an off-label prescription from their general practitioner, signaling a strong prevalence of the practice (Stewart et al., 2007). This study indicated that extemporaneous compounding is continuing in the UK as off label.

### ***2.7.3 Australia***

According to Feldschuh (2008), extemporaneous compounding is still taught as part of the pharmacy curriculum although it is practiced to a lesser extent by local pharmacists. In his review in 2008, of all products with approved paediatric indications, close to 24% were not available in a form suitable for administration for children. This report also indicated that metronidazole vaginal gel is an example of a product available overseas which is compounded by a pharmacist if required by an Australian patient (Feldschuh, 2008).

### ***2.7.4 New Zealand***

In the survey carried out by Kairuz et al. (2007a) on extemporaneous compounding in New Zealand hospitals it was revealed that extemporaneous preparation for oral use involved the reformulation of 74 drugs out of 2015 products over a period of seven months in seven hospitals. Medicines requiring extemporaneous preparation included reformulation of capsules (Ursodeoxycholic acid and Omeprazole), including Propranolol and Folic acid tablets. These solid dosage forms are crushed and suspended and made into a liquid oral dosage form. Midazolam, a bitter tasting medicine, is an example of a tablet crushed and suspended in a liquid. Other dosage forms in the form of powders such as Phenobarbitone sodium and Magnesium hydroxide were extemporaneously prepared. The off-label use of medicines was also reported. There were ten most frequently compounded medicines within the seven months of study in the seven hospitals out of the eleven which responded. These were Thyroxine, Metoprolol, Sucralfate, Hydrochlorothiazide, Amiodarone, Sotalol, Diazoxide, Ursodeoxycholic acid, Omeprazole and Propranolol. Furthermore, Omeprazole suspension was found to be compounded at all hospitals, while Ursodeoxycholic acid suspension was compounded for children at only one hospital which had a paediatric unit. Some of the medicines which were extemporaneously compounded were Allopurinol, Baclofen, Clobazam, Clonidine, Diazepam, Domperidone, Pilocarpine Nitrate and Terbinafine.

### ***2.7.5 United States of America***

Allen (2001) conducted a study in Oklahoma city where it was estimated that dermatological skin disorders occurred in 5% of the population, and extemporaneous

compounding could be beneficial for other routes of administration and different dosage forms other than oral could be used to accommodate the prescriber's specific needs.

## **2.8 Conclusion**

Most medicines which are manufactured by pharmaceutical industries are authorised for adult administration. There are, however, situations that dictate the manipulation or extemporaneous compounding of medicines for provision of healthcare to paediatrics, geriatrics and adults with swallowing difficulty to administer such medicines in a solid dosage form. Compounded medicines are prepared by a pharmacist who received teaching on compounding skills to prepare and to assure safety and quality of the final medicines. The above literature review emphasises the important role that extemporaneous compounded preparations play in meeting specific needs of patients. It also shows that this aspect of health care is being studied in several countries whilst none has been officially reported for South Africa. The review emphasises the global lack of quality testing on these preparations elevating the risks of their use in patients. There is a need for compounded medicines to be regulated with standardised methods of preparation. The compounding risks can be minimised through pharmacists' skills, training and knowledge on quality assurance procedures. Extemporaneous compounding, therefore, plays a critical role in optimising health care delivery and strategies to enhance its standards and control is important in any country.

## CHAPTER THREE: SUBMITTED MANUSCRIPT

### 3.1 Introduction

This article has been submitted to African Journal of Pharmacy and Pharmacology. See the proof for the manuscript submission (Annexure 1) and reports on the original research:

*Investigating extemporaneous compounding practices in the Polokwane tertiary hospital pharmacy in South Africa – a pilot study.*

Masupye E, Suleman F, Govender T (2015)

This chapter presents the submitted paper as per the journal stipulated format and limitations in terms of graphs, tables and word count.

Written permission to conduct the study was sought from and granted by the Research Ethics Committee of the University of KwaZulu-Natal, (HSS/0984/2009) (Annexure 2). See also the Limpopo provincial permission letter (Annexure 3) and the letter from the Chief Executive Officer of the hospital (Annexure 4). The following tools were used: Interview instrument for pharmacists' skills set; questionnaire (Annexure 5). See too the informed consent form (Annexure 6) and the compounded medicines data collection sheet (Annexure 7).

Ms E Masupye was responsible for proposal development, data collection and analyses (with the assistance of a statistician) and the write up. Prof F Suleman and Prof T Govender served as supervisor and co-supervisor respectively.

### **3.2 Submitted manuscript**

#### **Investigating extemporaneous compounding practices in the Polokwane tertiary hospital pharmacy in South Africa – a pilot study**

Euphenia Mathebule Masupye<sup>1,2</sup>, Fatima Suleman<sup>2</sup>, Thirumala Govender<sup>2</sup>

<sup>1</sup>Department of Pharmacy, University of Limpopo, Private Bag X1106, Sovenga, 0727, South Africa.

<sup>2</sup>Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal, Private Bag X54001, Durban, 4000, South Africa.

#### **Abstract**

Medicine availability is an important aspect of providing good quality health care. Some medicines are available in doses that are not suitable for a specific population group and therefore manipulation of the existing medication is undertaken in order to obtain the required concentration of that medication. Studies on the practices, frequency and extent of extemporaneous compounding have been undertaken in other countries such as New Zealand, Australia, United Kingdom, United States of America, Netherlands and Mexico. No data currently exists for South Africa. Therefore, the aim of this pilot study was to explore the extemporaneous compounding practices in a South African public sector setting. A quantitative research approach applying a cross-sectional research design was used in this study to determine the extemporaneous compounding practices in a tertiary hospital pharmacy. Twenty-five pharmacists responded to a questionnaire on their knowledge and practices. Data was collected from 691 batch records and prescriptions dating from the April 2008 to March 2009 to determine the frequency and extent of extemporaneous compounding. Data was analyzed using the Statistics Package for Social Sciences (SPSS version 20.0; 2011). Most (96%) of the pharmacy personnel indicated having received compounding training skills through supervision by experienced pharmacists. 72% explained that they compounded medication due to the unavailability of the prescribed drugs. Most (60%) of the respondents confirmed that the expiry date is personally developed. This study identified the need for more research into this practice and the use of

evidence from literature-based information for aspects like stability testing to assure the medicines' quality and compounding practice.

**Keywords:** Extemporaneous, compounding, quality, quality assurance,

## **Introduction**

The global and chronic lack of licensed medicines and appropriate dosage forms and strength for specific groups of patients is widespread and has sparked the initiation of extemporaneous compounding practice worldwide (Brion et al., 2003; Giam et al., 2012). The need for extemporaneous compounding is further observed in the case of a rare disease condition that requires a tailor-made therapy for a specific patient (Salgado et al., 2005; Spark, 2014). Other reasons for extemporaneous compounding are sensitivity/allergy to certain excipients and preservatives, different dose availability or different routes of administration required, or compliance problems related to the use of some medications, for example palatability of the formulation/medicine (Feldschuh, 2008; Spark, 2014). The dose or the dosage form registered as such might not be suitable or appropriate for paediatrics, geriatrics or those adults who are unable to swallow solid dosage forms and those for whom medication is administered in a liquid form through naso-gastric tubes due to poor swallowing reflexes necessitating extemporaneous compounding (Standing and Tuleu, 2005; Kairuz et al., 2007a; Giam et al., 2012). All these problems, coupled with pervasive lack of commercially available suitable drugs, have thus resulted in the need to make use of extemporaneous preparations in most hospital pharmacies.

Giam and McLachlan (2008) defined extemporaneous compounding as the extemporaneous preparation, mixing, packaging or labeling of a drug as the result of a practitioner's prescription drug in order to meet an individual patient's need. They may be formulated from existing dosage forms (Brion et al., 2003; Haywood and Glass, 2007; Spark, 2014) which entails crushing commercially available tablets and capsules contents into a suitable liquid dosage form with the aim of providing accessible essential medications to, amongst others, patients who are unable to swallow solid dosage forms (Nahata and Allen, 2008).

On the other hand, in the United States, the Food and Drug Administration (FDA) regards traditional pharmacy compounding as the extemporaneous combining, mixing, or altering of ingredients by a pharmacist in response to a physician's prescription to create a medication tailored to the specialized medical needs of an individual patient. Traditional compounding

typically occurs when a regulatory body-approved drug is unavailable or a licensed health care provider decides that an approved drug is not available in the appropriate dosage form for his or her patient's medical needs. Extemporaneous compounding may again occur in the case of the manipulation of the product's strength suitable for adult use, where the prescriber needs a lesser strength for an infant (Kairuz et al., 2007b).

Improperly compounded, adulterated drugs have the potential to cause significant harm to patients (Food and Drug Administration, 2006). The global lack of documented and standardized formulae (Sellers et al., 2012) poses a high risk to patients as there may be variation in manufacturing methods used. Furthermore, the excipients used may differ greatly and their effect on the stability and quality of the compounded product cannot be guaranteed. These studies emphasize that without strict observance of good manufacturing practice guidelines it is possible to have miscalculations of the respective quantities of each ingredient and this could be problematic especially where the system and processes are not tightly regulated.

A number of problems have been reported in recent years due to a lack of quality assurance processes. In the United States a 2012 meningitis outbreak was tied to the now-shut New England Compounding Center in Framingham that killed at least 64 people and sickened 750 more. Inspections subsequently found unsanitary conditions at the company's facility (Shaughnessy, 2012). Between March and April 2013, the FDA requested a number of voluntary nationwide recalls for compounded products due to a lack of sterility assurance (Food and Drug Administration, 2014). In South Africa, in the last decade, problems were also detected with the mixing of traditional medicines and conventional medicines that had serious adverse events (Snyman et al., 2005).

While most countries such as New Zealand (Kairuz et al., 2007a), Australia (Feldschuh, 2008), United Kingdom (Steward et al., 2007), United States of America (Treadway et al., 2007), Netherlands (Giam and McLachlan, 2008) and Mexico (Flores-Perez et al., 2008) have undertaken studies to determine the skills of staff compounding medicines, as well as the frequency and extent of extemporaneous compounding, no data exists for South Africa. Such studies are essential for improving the care of patients, especially because of the unique and complex health challenges in the country including the HIV/AIDS crisis and the compounding that takes place for paediatric preparations.

The purpose of this pilot study was to explore the extemporaneous compounding practices in South African public sector setting in order to evaluate the standards of compounding.

## **Materials and Methods**

This was a cross sectional descriptive pilot study, that was conducted in the Polokwane Municipality, which is in the Capricorn District of Limpopo Province, South Africa, and has 44% of the district population. The Province is situated in the north east of South Africa, covering a geographical area of 124 kilometers and is made up of five districts, namely: Vhembe, Mopani, Capricorn, Sekhukhuni and Waterberg. The Capricorn District has five municipalities (Statistics South Africa, 2007) in total. According to the Limpopo Department of Health and Social Development (2008) the Department operates and manages 49 hospitals with a population of 5,514 million and approximately 500 health care centres and clinics. These centres have approximately 11 400 beds, including 560 clinic beds. Of the 49 hospitals, six are regional and three specialized hospitals. Of the remaining forty, 38 are district hospitals and one Polokwane/Mankweng hospital complex with a combination of two hospitals - Pietersburg Campus and Mankweng Campus and a tertiary hospital with 470 beds. (Limpopo Department of Health and Social Development, 2008). The two hospitals forming the Polokwane/Mankweng hospital complex serves 47 other hospitals in the entire province.

A purposive selection was conducted to select the tertiary hospital in the province as the site of study. This was specifically due to the health professional specialization in this study area. A tertiary hospital is a referral hospital with a medical specialty mix at its disposal. It provides specialist level services and receives referrals from six regional hospitals, where a regional hospital provides health services in the fields of internal medicine, paediatrics, obstetrics, gynecology and general surgery on a 24-hour basis.

Pharmacists in the hospital settings are responsible for assuring the quality of all compounded preparations according to Nunn (2003). This is largely due to their professional obligation and training enabling them to perform extemporaneous compounding and also being cautious in making sure that all formulations are followed to the letter in order to maintain acceptable compounding standards. Compounding skill is a required competency for practice for registered pharmacists in many countries, more especially in New Zealand (Kairuz et al., 2007a).



Thus, a purposeful sampling was conducted to select the pharmacists. A self-administered close-ended and open-ended questionnaire was designed to collect information from the pharmacists and the pharmacy managers for characterization of the compounding practice processes for quality assurance on seven items, namely: a) the pharmacist's demography, b) the education level, c) class of personnel, d) training methods, e) procedures and policies for extemporaneous compounding, f) how expiry dates are determined and g) the most common reasons for undertaking extemporaneous compounding. The questionnaire was adopted from a previously used one and verified by Treadway et al. (2007) and then modified in this study to include additional variables. The questionnaire was designed to record the information required and piloted in a large hospital pharmacy department prior to undertaking the survey. It was completed on the pharmacists' spare time and final collection was after six months. The participants' identification was coded for anonymity. The pharmacists willing to participate in the study signed the consent form and completed the questionnaire after information about the study was explained by the researcher. The study was conducted between 1<sup>st</sup> January 2008 and 31<sup>st</sup> December 2009.

In order to assess the frequency and the extent of extemporaneous compounding in the hospital pharmacies of the Polokwane Municipality, retrospective data collected on a modified data sheet designed by Kairuz et al. (2007a) was initially used. A data collection sheet was designed to record the information required for this aspect of the study and piloted in a large hospital pharmacy department in the same district prior to undertaking the survey. All the batch records from April 2008 to 31st March 2009 were purposefully sampled. The data collection sheet was amended to provide the following information: the name of the compounded drug, strength, quantity produced, route of administration, dosage form, storage conditions, expiry date, date of preparation, and disease condition.

Retrospective data was collected on site using the data collection sheet which was formulated to determine the number of extemporaneously compounded preparations out of the total number of prescriptions for the period of the study, April 2008 to March 2009. This measured the extent of extemporaneous compounding. A purposeful sampling was conducted to select the prescriptions.

All extemporaneously compounded preparations in the data collection sheet were coded on a coding sheet and captured on Microsoft Excel<sup>®</sup>. All variables for assessing the frequency

and the extent of extemporaneous compounding were coded and captured as well on Microsoft Excel<sup>®</sup> (Version 12, released in 2007). The scale question was coded from “1” to “4” with “1” representing “Never” and “4” representing “Always”. “Yes” and “No” were coded such that “1” represented “Yes” and “2” represented “No”. All questionnaires were coded and captured on Microsoft Excel<sup>®</sup>. The analysis consisted of descriptive and analytical components. This was done using the Statistics Package for Social Sciences (SPSS Version 20, 2011).

### **Ethical Considerations**

Written permission to conduct the study was sought from and granted by the Research Ethics Committees (HSS/0984/2009) of the University of KwaZulu-Natal, The Limpopo Provincial Department of Health and Social Development and the hospital- Chief Executive Officers (CEO).

### **Results**

#### *Expertise of Personnel*

Fifty-nine questionnaires were distributed to tertiary hospital pharmacy personnel. Only 25 were returned, resulting in a 42.37% response rate. The low response rate was due to non-availability of respondents to participate because they verbally mentioned large daily workload as a reason.

The demographic profile of the sample depicted in Table 1 indicated that the majority of the pharmacists were female (56%) while 44% were male. Pharmacy personnel in the age range of 20 and 30 years made up 36% of the sample, while those in the age range 31 to 40 comprised 32% of the sample.

There was an equal distribution of senior pharmacists (20%) and the registered pharmacy assistants (20%) in the personnel category. With regard to the pharmacists' level of education, 64% indicated Bachelor of Pharmacy to be their highest level of education.

**Table 1 Demographic profile as percentages of the total sample**

<b>Variable</b>	<b>Number (n=25)</b>	<b>Frequency</b>	<b>Percent (%)</b>
Gender	Female	14	56%
	Male	11	44%
Race	Black	23	92.0%
	White	2	8.0%
Age (years)	20–30	9	36.0%
	31-40	8	32.0%
	41-50	7	28.0%
	51-60	1	4.0%
Personnel category	Principal pharmacist	4	16.0%
	Senior pharmacist	5	20.0%
	Pharmacist	3	12.0%
	Phamacist intern	4	6.0%
	Registered pharmacy assistant	5	20.0%
	Community pharmacist	2	8.0%
	Pharmacy assistant basic	2	8.0%
Personnel qualification	Doctorate	1	4.0%
	Bachelor of Pharmacy	16	64.0%
	Honours in Pharmacy (Post graduate courses)	8	32.0%

Almost all of the pharmacists (96%) indicated that they have received compounding training skills through supervision (80%), compared to 64% who stated that they received their experience via personal experience. Different findings of the training on compounding skills (69%) were reported in Texas by Treadway et al. (2007). Treadway and colleagues cited a study by Morris et al. (2002) with a training rate of 96% for pharmacists and 89% for

technicians. Training content (as outlined in Table 2) included information sourcing (56%), use of reference materials (68%), use of equipment like weighing scales, compounding tile for creams and ointments (96%), labelling according to recommended guidelines (92%), compounding record keeping (92%) and formulation record keeping (80%). A key finding in this study was the limited training in aseptic technique (12 %), which if not followed properly could result in contamination of compounded products with serious effects on patients.

**Table 2                      Compounding skills training areas**

Which training areas are covered in your training?	Agree		Disagree	
	Frequency	%	Frequency	%
Sourcing formulation	14	56	10	40
Use of references	17	68	8	32
Use of equipment, mortar and pestle, balances, etc	24	96	1	4
Labelling	23	92	2	8
Compounding record keeping	23	92	2	8
Formulation record keeping	20	80	5	20
Aseptic technique	3	12	22	88
Other	6	24	19	76

The pharmacy personnel were asked how often the following listed records were included in the documentation of their pharmacy. Their responses are shown in Table 3.

**Table 3                      Documentation of compounding in the hospital**

How often are the following listed records included in the documentation of this pharmacy?	Never	Sometimes	Often	Always
Manufacturing batch records	4%	8%	8%	80%
Compounding formulae and direction for compounding	8%	4%	16%	72%

A log of all compounded items	4%	8%	20%	64%
Balance - maintenance log books	64%	4%	12%	16%
Standard Operating Procedures	12%	8%	24%	52%

The study found 92% availability of compounding policies and procedures to ensure consistency in the production of the same product for different batches, compared to the findings by Treadway et al. (2007) of 71% in pharmacies in Texas. In the Treadway et al. (2007) study, two thirds of the pharmacies claimed to have no policies and procedures and did not provide staff training. Further, in this study (Table 3), there was no proof of records being kept on regular calibration of electronic weighing balances (76%) and maintenance (72%) despite the fact that documentation for compounding comprising of a manufacturing batch record are mostly kept (at 80%), as well as compounding formula and procedures (72%). A logbook of all compounded items was not kept in most instances (64%). The study further revealed that maintenance of the weighing balances was not carried out in most cases (64%).

**Table 4 Resources used for obtaining formulations in hospital pharmacy**

<b>What resources do staff members use for obtaining formulations in compounding?</b>	<b>%</b>	<b>Frequency</b>
Published literature	40%	10
Other hospitals	16%	4
Other pharmacies	4%	1
In-house; personally developed	28%	7
Missing	12%	3

Table 4 shows resources which the pharmacy personnel use for obtaining compounding formulations. There are conflicting results regarding self-reports on the source of compounding formulations from published literature (40%) in Table 4 versus self-reports on in-house formulations which are personally developed (28%). The verbal report from the

compounding pharmacists was that all the formulations used for compounding were self-derived. The hospital has compiled and used a formulation document containing the formulation of a product, method of preparation, quantities prepared, storage temperature, date of compounding and shelf-life. The results are in contradiction to those by Treadway et al. (2007) as in that study 82% used published literature and 40% were personally developed despite the emergence of more established sources for compounding formulations. In terms of determining an expiry date, the results shown in Table 5 revealed that 60% of the respondents confirmed that the expiry date was personally developed. There was inconsistency in documenting these dates. No stability and quality control tests were carried out to assess physical, chemical and microbiological changes or for the suitability of the formulation in terms of the active material content and shelf-life.

**Table 5 Establishing expiry dates**

	<b>N=19(6 missing 24%)</b>	
<b>Establishment of expiry dates</b>	<b>Agree</b>	<b>Frequency</b>
	<b>%</b>	
In-house stability testing	4%	1
External stability testing	4%	1
Recommendations from other hospital pharmacies	4%	1
Recommendations from other pharmacies	4%	1
Personally established dates	60%	15
Missing	24%	6

The pharmacy personnel were asked about the challenges they encounter in the preparation of compounded products. They strongly agreed (96%) that formulations were available in the pharmacy and that calculations were not (84%) a challenge. However, Standard Operating Procedures were not revised (72%). The main reasons for compounding were unavailability of a prescribed drug (72%), unsuitable dosage form (44%) and unsuitable route of administration (32%).

In Treadway et al.'s (2007) study on practices of pharmacies that compound extemporaneous formulations, unsuitable dosage form as a reason for compounding was found to be the lowest (16%) and cost at (50%) was the main reason for compounding.

While extemporaneous compounding practice processes are for improving compounding efficiency and effectiveness of compounded medicines, and to generate knowledge to compounders in order to help raise the standards of compounding and prevent the risk of patient harm, it was necessary to investigate what dosage forms and products were being compounded in Polokwane hospital pharmacies. This study, therefore, examined these aspects from batch records.

#### *The nature of products being compounded*

The results for the products being compounded were assessed by reviewing 691 batch records. There was an average of 27.64% preparations compounded per month. Solutions accounted for 43.9 % of the most frequently compounded dosage forms. This study revealed that dermatological preparations, that is, creams and ointments totalling 33.0% and 13.60% respectively (46.60%) are mostly compounded at the hospital. In a study by Buurma et al. (2003) who evaluated the frequency of compounding in the Dutch community pharmacies, the findings were that it consisted largely of dermatological preparations and dermatological dosage forms. A contrary result was found by Kairuz et al. (2007a) in the New Zealand hospital sample survey in determining the extent and nature of compounding, where oral suspensions were the most compounded dosage form with a reformulation of Omeprazole being the most frequently compounded drug.

The most compounded product was Betamethasone (27.9%). The shelf-life given for extemporaneously compounded preparations was found to be range from six months at 66.3%, three months at 14.5% to 12 months (9.8%). According to Brion et al. (2003) an unpublished UK survey showed that 54% of 112 pediatric extemporaneous formulations had inadequate data on shelf-life. This is due to lack of extensive research that will need to be undertaken to establish the suitability of the formulation on its stability.

A considerable number (98.30%) of extemporaneously compounded preparations were reported to be stored below 25°C. Only a small number (1.70%) were refrigerated at 2°C - 8°C. The refrigerated solutions were found to be the oral solutions containing minerals for supplementation. The other dosage forms and other oral and non-oral solutions were stored

below 25°C. Most of the preparations were extemporaneously prepared from commercially available drugs where the prescriber needed a lesser strength for a specific patient condition, irrespective of the patient's age.

## **Discussion**

Compounding errors are an emerging and serious problem. Pharmacists hold a unique position as health professionals who are formally trained in compounding medications and are licensed to dispense them.

This research attempted to gain an understanding of compounding practices in the tertiary hospital pharmacies in the Polokwane Municipality as confirmed by the study by Treadway et al. (2007) that confirmed that there are serious questions about the quality of compounded preparations. Most of the pharmacists in this study received their training as part of the undergraduate curriculum. A study by Eley and Birnie. (2006) indicates that pharmacy students do not adequately retain compounding knowledge and skills, and that pharmacy students' level of competency and retention of knowledge with respect to compounding capsules is not adequately retained after a 12-month hiatus. There is thus a need to look at competency assessments for compounding pharmacists as well as continuous professional development in this area.

This study indicated that extemporaneous compounding is not subjected to a quality control procedure beyond calculations, ingredients checking and visual inspection which is in agreement with the findings from Donnelly et al. (2008). This is in contrast to the quality control operations pertaining to proprietary products manufactured by the pharmaceutical industry, where GMP standards are followed (Donnelly et al., 2008).

There have been attempts in the past decade, according to Treadway et al. (2007), to raise the standard of all compounding practices through the efforts of the United States Pharmacopeia (USP) and the American Society of Health-System Pharmacists (ASHP) through ASHP guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products in 2000. More recently, the USP has implemented further procedures and requirements on compounding non-sterile and sterile preparations in an attempt to help raise the standards of compounding and prevent the risk of patient harm. This is largely absent in South Africa.



Our study indicated a frequency of compounding at this hospital as being between 40%-50%. In the United States it has been estimated that approximately 1% of prescriptions are compounded, representing nearly 30 million prescriptions annually. A similar estimate has been made for compounded prescriptions produced in Australia (Giam et al., 2012).

Our study revealed that pharmacy compounding consists mostly of dermatological products and dermatological dosage forms. This data confirms results from Buurma et al. (2003). Another study in New Zealand hospitals by Kairuz et al. (2007a) revealed suspensions to be the mostly compounded preparations with creams, ointments and non-oral solutions being the most commonly prepared. The shelf-life given for extemporaneously compounded preparations was found to be three months, six months and 12 months. However there are some products which should be used within 24 hours of preparation. According to Brion et al. (2003) an unpublished UK survey showed that 54% of 112 pediatric extemporaneous formulations had inadequate data on shelf-life. This suggests that extensive research needs to be undertaken to establish the suitability of the formulation on its stability. Lack of time, expertise and facilities in hospital pharmacies, among other factors, limit the undertaking of such research.

## **Conclusions**

There is a need for professional organizations to play a role in extemporaneous compounding as a source of compounding formulations and quality assurance guidelines. This could be a way to increase the quality of available formulas by using a central source of information as well as guidelines for expiry date determination and equipment calibration among other quality assurance processes. There is a need for more research on the compounding practices in both public and private sector facilities in South Africa.

Further research on internationally harmonized guidelines for extemporaneous compounding to supplement formulation development needs should be established, as in countries like the USA where the ASHP has developed guidelines on standards of compounding to prevent the risk of patient harm. In South Africa, like all other countries, there is a need to train pharmacists on compounding skills and to regulate and standardize extemporaneous compounding to avoid usage of varying formulation methods.

## References

- Brion F, Nunn AJ, Rieutord A (2003). Extemporaneous (magistral) preparation of oral medicines for children in European hospitals. *Acta Paediatrica* 92:486-90.
- Buurma H, de SmeTP, van den Hoff OP, Sysling H, Storimans M, Egberts ACG (2003). Frequency, nature and determinates of pharmacy compounded medicines in Dutch community pharmacies. *Pharmacy World and Science* 25(6):280-287.
- Donnelly R, McNally M, Barry J (2008). Is extemporaneous dispensing really in the best interest of patients? *The Pharmaceutical Journal* 280:251-254.
- Eley JG, Birnie C (2006). Retention of compounding skills among Pharmacy students. *American Journal of Pharmaceutical Education* 70(6):132.
- Feldschuh M (2008). Compounding in community pharmacy. *Australian Prescriber* 31(2):30-31.
- Food and Drug Administration (2014). Martin Avenue Pharmacy, Inc. Compounded Sterile Preparations, Recall – Lack of Assurance of Sterility. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm412493.htm>. Last accessed, 12 May 2015.
- Food and Drug Administration (2006). 2006 Limited FDA Survey of Compounded Drug Products. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm> Last accessed 21 January 2015.
- Flores-Perez C, Flores-Perez J, Juarez-Olguin H, Barranco-Garduano D (2008). Frequency of drug consumption and lack of pediatric formulations. *Acta Pediatrica de Mexico* 29(1):16-19.
- Giam J, McLachlan AJ (2008). Extemporaneous product use in paediatric patients: a systemic review. *International Journal of Pharmacy Practice* 16:3-10.
- Giam JA, McLachlan AJ, Krass I (2012). Characterizing specialized compounding in community pharmacies. *Research in Social and Administrative Pharmacy* 8(3):240-252.
- Gross Z (2005). Why special manufacturing units are needed now as much as they were ever. *The Pharmaceutical Journal* 275:743-744.

Haywood B, Glass A (2007). Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. *Journal of Pharmacy Practice and Research* 37:131-133.

Kairuz T, Chhim S, Hasan F, Kumar K, Lal A, Patel R, Singh R, Dogra M, Garg S (2007a). Extemporaneous compounding in a sample of New Zealand hospitals: a retrospective survey. *The New Zealand Medical Journal* 120:1251.

Kairuz TE, Gargiulo D, Bunt C, Garg S (2007b). Quality, safety and efficacy in the 'Off-Label' use of medicines. *Current Drug Safety* 2:89-95.

Limpopo Department of Health and Social Development (2008). Final Limpopo DHSD 2008/09 -11 Annual Performance Plan - Vote 7. Republic of South Africa: Limpopo Provincial Government.

Morris AM, Schneider PJ, Pederson CA, Mirtallo JM (2003). National survey of quality assurance activities for pharmacy-compounded sterile preparations. *American Journal of Health-System Pharmacy* 60(24):2567-76.

Nahata MC, Allen LV (2008). Extemporaneous Drug Formulations. *Clinical Therapeutics* 30(11):2112-2119.

Nunn AJ (2003). Making medicines that children can take. *Archives of Disease in Childhood* 88:369-371.

Salgado AC, Rosa ML, Duarte MA, Almeida AJ (2005). Stability of spironolactone in an extemporaneously prepared aqueous suspension: the importance of microbiological quality of compounded paediatric formulations. *The European Journal of Hospital Pharmacy Science* 11(3):68-73.

Schultz M (2007). Compounding products in a non-manufacturing environment. *Health Science Academy Professional practice* 7(2):4-6.

Shaughnessy AF (2012). Meningitis outbreak shines light on compounding pharmacies. *British Medical Journal* 345:e7432.

Snyman T, Stewart MJ, Grove A, Steenkamp V (2005). Adulteration of South African traditional herbal remedies. *Therapeutic Drug Monitoring* 27(1):86-89.

Spark MJ (2014). Compounding of medicines by pharmacies: an update. *Maturitas* 78:239-240.

Standing J, Tuleu C (2005). Paediatric formulations – getting to the heart of the problem. *Journal of Pharmaceutics* 300:55-56.

Sellers S, Utian WH (2012). Pharmacy Compounding Primer for Physicians: *Prescriber Beware Drugs* 72.16:2043–2050. <http://link.springer.com/article/10.2165/11640850-000000000-00000#page-1>. Last accessed, 30 March 2015.

Statistics South Africa (2007). Community Survey, 2007 Basic Results: Municipalities. Statistical release P0301.1.

Steward D, Rou FA, Snaith A, Elliot K, Peter J, and McLay H and J (2007). Attitude and experiences of community pharmacists towards pediatric off-label prescribing: a prospective survey. *British Journal of Clinical Pharmacology* 64(1):90-95.

Treadway A, Craddock D, Leef R (2007). Practices of Pharmacies that compound extemporaneous formulations. *American Journal of Health Systems Pharmacy* 64:1403-1409.

## **CHAPTER FOUR: CONCLUSIONS AND RECOMMENDATIONS**

### **4.1 Introduction**

In this chapter conclusions from the findings of the study are drawn and limitations of the study and recommendations for future research and strategies to improve or maintain the compounding practice are proposed. The aim of this pilot study was to explore extemporaneous compounding practices in a South African public sector setting in order to help evaluate the standards of compounding. The findings are discussed in accordance to the objectives of the study.

### **4.2 Conclusions**

#### **4.2.2.1 To assess the skills set and capacity of the staff compounding medicines in the tertiary hospital pharmacy in the Polokwane Municipality.**

In this pilot study, it was observed that the majority of the pharmacists were receiving compounding skills training through supervision by experienced pharmacists on the use of equipment like the mortar and pestle and weighing of balances, yet the maintenance of the weighing balances was not carried out in most instances. Also, there were no stability and quality control tests carried out to assess physical, chemical and microbiological changes or for the suitability of the formulation in terms of the active material content and shelf-life. Expiry dates were personally developed. Another finding was the limited training in aseptic technique. There was also no proof of records kept on regular calibration and maintenance of electronic weighing balances, despite the fact that documentation for compounding in terms of manufacturing batch record were largely kept. A logbook of all compounded items was also not kept.

#### **4.2.2.2 To identify the most common dosage form and product being compounded in the tertiary hospital pharmacy in the Polokwane Municipality.**

This pilot study revealed that small scale extemporaneous compounding is occurring in a tertiary hospital pharmacy in the Polokwane Municipality. Dermatological creams are the most frequently compounded category of medicines currently. A considerable number of

solutions, both oral and those used for disinfection or used as an antiseptic, were also compounded.

### **4.3 Limitations of the study**

The aim of this pilot study was to determine the extemporaneous compounding practice in a South African public sector hospital setting. The methods employed to generate the findings in this study were in line with those employed in other studies. However, certain limitations as described below should be noted:

- The results from only one tertiary hospital does not constitute a large enough sample to draw firm conclusions about the practice in the entire province and South Africa.
- The patients' information regarding age and disease condition were not available from the file and could not be captured. The availability of such information on documentation of extemporaneous compounding improves the availability of information on medicines for different patients' needs and for future modification of existing dosage forms by researchers to ensure maximal therapeutic responses.

### **4.4 Recommendations for future work**

The following recommendations may be considered for further extemporaneous compounding studies:

**RESEARCH:** This pilot study gives some indications regarding the level of competence of the extemporaneous compounding staff as well as extemporaneous compounding practices at the tertiary hospital pharmacy in the Polokwane Municipality. The findings suggest that a wider in-depth research at a national level should be explored to determine the need for quality control in compounding practices and competence of staff. Further research on a national level to determine the frequency and extent of the compounding practice in both public and private sector facilities in South Africa and Africa will be important. Further investigations into the formulae used when compounding is needed as most may not be from published literature due to lack of compounding standards.

**GUIDELINES/POLICIES/REGULATIONS:** The study has shown the lack of stability studies on the compounded medicines, which hints at the need to prepare guidelines on good pharmaceutical practice in hospital and community pharmacies in relation to extemporaneous preparation in order to use a uniform standard. It further suggests research on internationally harmonized guidelines for extemporaneous compounding to supplement formulation development, and for professional organizations to play a role in extemporaneous compounding as a source of compounding formulations.

**EDUCATION:** The pharmacy undergraduate curriculum may need to be reviewed for relevance of content related to the compounding practice, which is suggested by the low aseptic technique skill shown in this pilot study.

#### **4.5 General Conclusions**

Stability and quality control tests carried out to assess physical, chemical and microbiological changes for the suitability of the formulation in terms of the active material content and shelf-life are considered to be a needful necessity since there have been none carried out so far. The recommendations for further research on internationally harmonized guidelines for extemporaneous compounding to supplement formulation development as well as the dire need to further train pharmacists on compounding skills (including the aseptic technique) and to regulate and standardize extemporaneous compounding so as to avoid usage of varying formulation methods are of utmost importance and therefore they need to be implemented.

#### **4.6 Declaration of interest**

The author reports no conflict of interest.

## REFERENCES

Allen LV Jr. Editor-in-Chief. Remington: The Science and Practice of Pharmacy. 22nd ed. Chicago: Pharmaceutical Press; 2012.

Arghahowa SE, Egharevba JO, Okon F (2013). Patterns of extemporaneous prescriptions and preparations in tertiary health institutions: a five year Assessment. *International Journal of Pharmaceutical Compounding* 17(5):432-5.

Argoff CE, Kopecky EA (2014). Patients with chronic pain and dysphagia (CPD): unmet medical needs and pharmacologic treatment options. *Current Medical Research and Opinion* 30(12):2543-2559.

Aspden TJ, Rew A, Anderson C, Tan J, Woodrow R, Zheng Y 9th International Conference: Life Long Learning in Pharmacy (2011). 'An investigation into the teaching of extemporaneous compounding skills to pharmacy students in schools of pharmacy in Australia, Canada, New Zealand, South Africa and the United Kingdom'.

<https://researchspace.auckland.ac.nz/handle/2292/17111?show=full>

Aquilina A (2013). The extemporaneous compounding of paediatric medicines at Mater Dei Hospital. *Journal of the Maltese College of Pharmacy Practice* Issue 19.

<http://www.mcphpnet.org/publications/issue19-9.pdf>. Last accessed, 26 April 2015.

Barnes PW (2008). Inside the medicines cabinet: making children's medicine a grown-up issue. *Journal of Pharmaceutical Sciences* 97(12):5074-9.

Brion F, Nunn AJ, Rieutord A (2003). Extemporaneous (magistral) preparation of oral medicines for children in European hospitals *Acta Paediatrica* 92: 486-90.

Breitkreutz J (2008). European perspectives in pediatric formulations. *Clinical Therapeutics* 30(11): 2133-45.

Butler N (2006). Quantifying dispensing services in South Africa-a pilot project. In: 14<sup>th</sup>



International Social Pharmacy Conference: Public Health, St Anne's College, Oxford, 11 – 14 July 2006). Abstract retrieved from <http://www.sapj.co.za/index.php/SAPJ/article/viewFile/72/70>. Last accessed, 12 May 2015.

Buurma H, de Smet P, van den Hoff OP, Sysling H, Storimans M, Egberts ACG (2003). Frequency, nature and determinates of pharmacy compounded medicines in Dutch community pharmacies. *Pharmacy World and Science* 25(6):280-87.

Calvalho M, Tuleu C, Taylor KM (2008). Current compounding practices in Europe. *International Journal of Pharmaceutical Compounding* 12(2):94-97.

Canadian Good Manufacturing Guidelines (2009). [http://www.hc-sc.gc.ca/dhdp-mps/alt\\_formats/pdf/compli-conform/gmp-bpf/docs/gui-0001\\_eng.pdf](http://www.hc-sc.gc.ca/dhdp-mps/alt_formats/pdf/compli-conform/gmp-bpf/docs/gui-0001_eng.pdf). Last accessed 04 March 2015.

Chowdhury C, Taylor K, Harding G (2003). Teaching extemporaneous preparation in UK schools of pharmacy. *Pharmacy Education* 3(4):229-36.

Chowdhury T, McLachlan AJ, Krass I (2012). Characterizing specialized compounding in community pharmacies. *Research in Social and Administrative Pharmacy* 8 (3):240-252. [http://www.rsap.org/article/S1551-7411\(11\)00073-8/pdf](http://www.rsap.org/article/S1551-7411(11)00073-8/pdf). Last accessed, 27 April 2015.

Cox Wellness Center report. Custom Compounding Services. (2005). <http://www.coxpharmacy.com/compounding/custom/asp>. Last accessed, 22 May 2010.

Crawford SY, Dombrowski SR (2008). Extemporaneous compounding activities and the associated informational needs of pharmacies. *American Journal of Hospital Pharmacy* 486: 1205-10.

de Villiers J (2005). Innovations in extemporaneous compounding. In: 26th Annual Conference of the Academy of Pharmaceutical Sciences: Innovations in Pharmaceutical Sciences, Port Elizabeth, South Africa, 29 September-01 October 2005. Combination antiretroviral therapy: Formulation of a powder for oral suspension containing Lamuvudine,

Zidovudine, and Nevirapine.

<http://www.sapj.co.za/index.php/SAPJ/article/viewFile/215/207>. Last accessed, 8 May 2015

Donnelly R, McNally M, Barry J (2008). Is extemporaneous dispensing really in the best interest of patients? *The Pharmaceutical Journal* 280:251-254.

Eley JG, Birnie C (2006). Retention of compounding skills among pharmacy students. *American Journal of Pharmaceutical Education* 70(6):132.

European Medicinal Agency EMEA/H/8227/02 (2002) – Guideline on the investigation of medicinal products in the term and preterm neonates.

Food and Drug Administration (2006). 2006 Limited FDA Survey of Compounded Drug Products.

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm>. Last accessed 21 January 2015.

Feldhschuh M (2008). Compounding in community pharmacy. *Australian Prescriber* 31(2):30-31.

Flores-Perez C, Flores-Perez J, Juarez-Olguin H, Barranco-Garduano D (2008). Frequency of drug consumption and lack of pediatric formulations. *Acta Pediatric de Mexico* 29(1): 16-19.

Giacoa G, Taylor-Zapara P, Mattison D (2008). Eunice Kennedy Shriver National Institute of Child Health and Human Development Pediatric Formulation Initiative. *Clinical Therapeutics* 30:2097-101.

Giam J, McLachlan JA (2008). Extemporaneous product use in paediatric patients: a systemic review. *International Journal of Pharmacy Practice* 16:3-10.

Giam AJ, McLachlan A, Krass I (2011). Community pharmacy compounding – impact on professional status. *International Journal of Clinical Pharmacy* 33(2): 177-182.

Giam JA, McLachlan AJ, Krass I (2012). Characterizing specialized compounding in community pharmacies. *Research in Social and Administrative Pharmacy* 8(3): 240-252.

Glass BD, Haywood A (2006). Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. *Journal of Pharmaceutical Science* 9(30): 398-496.

Gross Z (2005). Why special manufacturing units are needed now as much as they were ever. *The Pharmaceutical Journal* 275:743-744.

Gudeman J, Jozwiakowski M, Chollet J, Randell M (2013). Potential risks of pharmacy compounding. *Drug in R&D* 13(1): 1 – 8. <http://link.springer.com/article/10.1007/s40268-013-0005-9#>. Last accessed, 31 March 2015.

Harris T, Adebayo AS, Bennett D, Olugbuyi O, Scott C. Extemporaneous Compounding of Captopril for Managing Cardiac Conditions in Children at a Major Paediatric Hospital in Jamaica. “R6359” paper presented at: AAPS Annual Meeting and Exposition, Sandiego Convention Center. 2-6 November 2014  
<https://2014aapsam.zerista.com/poster/member/24057>. Last accessed, 5 May 2015.

Jooste N (2011). Extemporaneous preparation in a resource-limited setting: sildenafil citrate suspension. *South African Pharmaceutical Journal* 78 (8):49-50.  
<http://www.sapj.co.za/index.php/SAPJ/article/view/1141/1461>. Last accessed, 5 May 2015.

Haywood B, Glass A (2007). Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. *Journal of Pharmacy Practice and Research* 37:131-33.

Kairuz T, Chhim S, Hasan F, Kumar K, Lal A, Patel R, Singh R, Dogra M, Garg S (2007a). Extemporaneous compounding in a sample of New Zealand hospitals: a retrospective survey. *The New Zealand Medical Journal* 120:1251.

Kairuz TE, Gargiulo D, Bunt C, Garg S (2007b), 2007. Quality, safety and efficacy in the 'off-label' use of medicines. *Current Drug Safety* 2: 89-95.

Kadi A, Francioni-Proffitt D, Hindle M, Soine W (2005). Evaluation of basic compounding skills of pharmacy students. *American Journal of Pharmaceutical Education* 69(4):508-14.

Kolling WM, McPherson TB (2013). Assessment of the accuracy of pharmacy students' compounded solutions using vapor pressure osmometry: Instructional Design and Assessment. *American Journal of Education* 77(3): Article 58.

Labuschagne JW, du Preez JL, Lotter AP (2006). Innovations in extemporaneous compounding. In: 26th Annual Conference of the Academy of Pharmaceutical Sciences: Innovations in Pharmaceutical Sciences, Port Elizabeth, South Africa, 29 September-01 October 2005. The formulation and stability of dispersible or chewable tablets containing anti retroviral drugs. Abstract retrieved from <http://dspace.nwu.ac.za/handle/10394/1/browse?value=Labuschagne%2C+Joseph+Willem&type=author>. Last accessed, 7 May 2015.

Lau ETL, Steadman KJ, Mak M, Cichero JAY, Nissen LM (2015). Prevalence of swallowing difficulties and medication in customers of community pharmacists. *Journal of Pharmacy Practice and Research* 45(1):18-23.

Lee J, Redzuan A, Shah NM (2013). Unlicensed and off-label use of medicines in children admitted to the intensive care units of a hospital in Malaysia. *International Journal of Clinical Pharmacy* 35(6):1025-1029. <http://link.springer.com/article/10.1007/s11096-013-9846-0>.

Limpopo Department of Health and Social Development (2008). Final Limpopo DHSD 2008/09 -11 Annual Performance Plan - Vote 7. Republic of South Africa: Limpopo Provincial Government.

Lowey A, Jackson M (2008). How to ensure the quality and safety of unlicensed oral medicines. *The Pharmaceutical Journal* 281:240.

McCague P, McElnay J, Donnelly R (2011). What are your views on specials and extemporaneous medicines preparation. *The Pharmaceutical Journal*.  
<http://www.pharmaceutical-journal.com/news-and-analysis/news/what-are-your-views-on-specials-and-extemporaneous-medicines-preparation/11102745.article>. Last accessed, 12 May 2015.

Magalhaes J, Rodrigues AT, Roque F, Figueiras A, Falcao A, Herdeiro MT (2015). Use of off-label and unlicensed drugs in hospitalised paediatric patients: a systemic review. *European Journal of Clinical Pharmacology* 71(1): 1-13.

Manrique YJ, Lee DJ, Islam F, Nissen LM, Cichero JAY, Stokes J, Steadman KJ (2014). Crushed tablets: Does the administration of food vehicles and thickened fluids to aid medication swallowing alter drug release? *Journal of Pharmaceutical Science* 17(2): 207-219.

Milne C, Bruss JB (2008). The economics of pediatric formulation development for off-patent drugs. *Clinical Therapeutics* 30(11):2133-45.

Nahata C, Morosco S, Lequire E (2000). Development of two stable oral suspensions of Levodopa-Carbidopa for children with amblyopia. *Journal of Pediatric Ophthalmology and Strabismus* 37:333-37.

Nahata MC, Allen LV (2008). Extemporaneous drug formulations. *Clinical Therapeutics*. 30(11): 2112-2119.

Nunn AJ (2003). Making medicines that children can take. *Archives of Disease in Childhood* 88:369-371.

Oceania Health Consulting (2005) . Review of the need for further regulation of extemporaneous compounding. <http://www.tga.gov.au/pdf/archive/review-ncctg-compounding-050921.pdf>. Last accessed 22 May 2009.

Patel VP, Desai TR, Chavda BG, Katira RM (2011). Extemporaneous dosage form for liquids. *Pharmacore: An International Research Journal* 2(2):86-103. <http://www.pharmacophorejournal.com/> Last accessed, 12 May 2015.

Patent google (2011). Stable liquid oily ready-to-use formulation, preparation thereof and use thereof. Publication number: WO2011128783 A2. <https://www.google.com/patents/WO2011128783A2?cl=en>. Last accessed, 21 May 2015.

Phan H, Leder M, Fishley M, Moeller M, Nahata M (2010). Off-label and unlicensed medication use and associated adverse drug events in a pediatric emergency department. *Pediatric Emergency Care* (26)6:424-430.

Prot-Labarthe S, Bussieres J, Brion F, Bourdon O (2007). Comparison of hospital pharmacy practice in France and Canada: can different practice perspectives complement each other? *Pharmacy World Science* 29:526-533.

Riley RJ. (2015). The Regulation of Pharmaceutical Compounding and the Determination of Need: Balancing Access and Autonomy with Patient Safety. <http://dash.harvard.edu/bitstream/handle/1/8852177/Riley.html?sequence=1>. Last accessed, 27 April 2015.

Salgado AC, Rosa ML, Duarte MA, Almeida AJ (2005). Stability of spironolactone in an extemporaneously prepared aqueous suspension: the importance of microbiological quality of compounded paediatric formulations. *The European Journal of Hospital Pharmacy Science* 11(3): 68-73.

Schultz M (2007). Compounding products in a non-manufacturing environment. *Health Science Academy Professional Practice* 7(2):4-6.

Sellers S, Utian WH (2012). Pharmacy Compounding Primer for Physicians: *Prescriber Beware Drugs* 72.16:2043-2050. <http://link.springer.com/article/10.2165/11640850-000000000-00000#page-1>. Last accessed, 30 March 2015.

Sosnik A, Seremeta K, Imperiale JC, Chiappetta DA (2012). Novel formulation and drug delivery strategies for the treatment of pediatric poverty-related diseases. *Drugs* 9 (3): 303-323.

Spark MJ (2014). Compounding of medicines by pharmacies: an update. *Maturitas* 78:239-240.

Staes C, Jacobs J, Mayer J, Allen J (2013). Description of outbreaks of healthcare associated infections related to compounding pharmacies, 2000-2012. *American Journal of Health-System Pharmacy* 70(15):10.2146/ajhp 130049.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3886339>. Last accessed, 29 January 2015.

Standing J, Tuleu C (2005). Paediatric formulations – getting to the heart of the problem. *Journal of Pharmaceutics* 300: 55-56.

Steinborn L (2004). GMP/ISO quality audit manual for healthcare manufacturers and their suppliers-(Regulations, Standards, and Guidelines): Regulations, Standards, and Guidelines (6th Ed). CRC Press Publishers.

[https://books.google.co.za/books?id=0TNQi5qn\\_TgC&pg=PA237&lpg=PA237&dq=Steinborn#v=onepage&q=Steinborn&f=false](https://books.google.co.za/books?id=0TNQi5qn_TgC&pg=PA237&lpg=PA237&dq=Steinborn#v=onepage&q=Steinborn&f=false). Last accessed, 21 May 2015.

Stewart D, Rouf A, Snaith A, Elliot K, Peter J, McLay H, McLay J (2007). Attitude and experiences of community pharmacists towards pediatric off-label prescribing: a prospective survey. *British Journal of Clinical Pharmacology* 64(1):90-95.

The United States Pharmacopoeia (2014). Pharmaceutical compounding – Nonsterile preparations. Chapter 795.

Tetty-Amlalo R (2005). Innovations in extemporaneous compounding. In: 26th Annual Conference of the Academy of Pharmaceutical Sciences: Innovations in Pharmaceutical Sciences, Port Elizabeth, South Africa, 29 September-01 October 2005. In vitro release of ketoprofen from proprietary and extemporaneously manufactured gels. <http://www.sapj.co.za/index.php/SAPJ/article/viewFile/215/207>. Last accessed, 8 May 2015.

Treadway A, Craddock D, Leef R (2007). Practices of pharmacies that compound extemporaneous formulations. *American Journal of Health Systems Pharmacy* 64:1403-1409.

Winfield AJ (2004). Dispensing techniques: Compounding and good practice. Winfield, AJ and Richards, RME (Eds). *Pharmaceutical Practice*. Churchill Livingstone. Edinburgh. UK.. (3rd Ed.). Singapore: Longman Singapore Publishers.

World Health Organisation (2007). Promoting Safety of Medicines for Children. [http://www.who.int/medicines/publications/essentialmedicines/Promotion\\_safe\\_med\\_childr\\_ens.pdf](http://www.who.int/medicines/publications/essentialmedicines/Promotion_safe_med_childr_ens.pdf). Last accessed, 8 May 2015.



## LIST OF ANNEXURES

### ANNEXURE 1: Confirmation for submission of Manuscript

From: African Journal of Pharmacy and Pharmacology [mailto:ajpp@academicjournals.org]

Sent: 27 January 2015 07:13 PM

To: Masupye, Euphenia

Subject: Manuscript Update On AJPP/27.01.15/4282: Current Status - Acknowledgement

#### African Journal of Pharmacy and Pharmacology

Dear Ms. Masupye Euphenia Mathebule

Your manuscript has been received by our Editorial Office and we have commenced the processing of the manuscript. You will be able to monitor the progress of your manuscript by using our manuscript management portal on <http://ms.academicjournals.me/> Kindly login as an author.

Author(s) Agreement

#### **Introduction**

This Author(s) Agreement become effective when you submit a manuscript to any of our journals

The terms of the Author(s) Agreement may change from time to time and the latest version applies to you when you submit a manuscript.

You must know, understand and comply with the Author(s) Agreement as well as the Instruction for Authors in each journal.

#### **Terms of the Author(s) Agreement**

1. Submitted manuscripts must be an original work of the author(s).
2. All referenced works should be adequately cited in the manuscript
3. The manuscript has not been previously published either in part or in full
4. The manuscript has not been submitted to another journal and or the manuscript is not undergoing evaluation and publication in another journal
5. All authors have contributed sufficiently to the work of the manuscript to justify their inclusion in the authorship of the manuscript.
6. All authors have reviewed the final version of the manuscript and approved it for submission to the journal.
7. Adequate permission has been requested and received by the author(s) for all data/information in the manuscript and as such, the manuscript is not infringing on any copyrights or classified information
8. The manuscript is submitted with the full knowledge and approval of all the sponsors/grants that provided funding/resources for the development of the manuscript
9. All errors discovered in the manuscript after submission is swiftly communicated to the

Editorial Office of the journal

10. All authors agree to receive periodic communication from the editorial office of the journal
11. Author(s) agrees to pay the required manuscript handling fee for each submitted manuscript

Kindly contact [helpdesk@academicjournals.org](mailto:helpdesk@academicjournals.org) if  
href="<mailto:helpdesk@academicjournals.org>">[helpdesk@academicjournals.org](mailto:helpdesk@academicjournals.org) if you have any queries

Thank you once again for submitting your manuscript to our journal.

Date	27-Jan-2015
Manuscript Number	AJPP/27.01.15/4282
Manuscript Title	Investigating extemporaneous compounding practices in the Polokwane tertiary hospital pharmacies in South Africa – a pilot study
Current Status	Acknowledgement
Corresponding Author	Suleman Associate Professor, Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal (Westville Campus), Private Bag X54001, Durban, 4000, KwaZulu-Natal, South Africa. <a href="mailto:sulemanf@ukzn.ac.za">sulemanf@ukzn.ac.za</a>



[View Archive](#)

#### Contacts Us

Editorial Office: [ajpp@academicjournals.org](mailto:ajpp@academicjournals.org)

Accounts Unit: [accounts@academicjournals.org](mailto:accounts@academicjournals.org)

Help Desk: [helpdesk@academicjournals.org](mailto:helpdesk@academicjournals.org)

Submit manuscripts: [ms.academicjournals.org/](https://ms.academicjournals.org/)

Website: [www.academicjournals.org/](http://www.academicjournals.org/)

**Thank you for submitting your manuscript to the African Journal  
of Pharmacy and Pharmacology**

**academicJournals**

## ANNEXURE 2: Ethics Committee letter of approval



12 December 2009

Mrs E Masupye  
P O Box 1140  
FAUNA PARK  
0787

Dear Mrs Masupye

**PROTOCOL: Evaluation of Extemporaneous Compounding in Polokwane hospital pharmacies**

**ETHICAL APPROVAL NUMBER: HSS/0984/2009: Faculty of Health Sciences**

In response to your application dated 02 December 2009, Student Number: **208573748** the Humanities & Social Sciences Ethics Committee has considered the abovementioned application and the protocol has been given **FULL APPROVAL**.

**PLEASE NOTE:** Research data should be securely stored in the school/department for a period of 5 years.

I take this opportunity of wishing you everything of the best with your study.

Yours faithfully


**Professor Steve Collings (Chair)**  
**HUMANITIES & SOCIAL SCIENCES ETHICS COMMITTEE**

SC/sn

cc: Mr G T Mahlatsi  
cc: Prof. T. Govender  
cc: Mr S Reddy

### ANNEXURE 3: Letter of approval to conduct the study in the province

PHD 094(1)



# LIMPOPO

PROVINCIAL GOVERNMENT  
REPUBLIC OF SOUTH AFRICA

---

**DEPARTMENT OF HEALTH & SOCIAL DEVELOPMENT**  
**POLOKWANE/MANKWENG HOSPITAL COMPLEX**

CAMPUS: ☒ PIETERSBURG ☐ MANKWENG

ENQUIRIES: ...**Dr. Khoabane R.S.**... TELEPHONE NO: **015 287 5014**.....

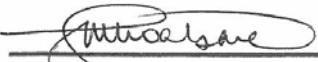
REFERENCE NO: .....**Ref: 44/1/3**... DATE: .....**20 July 2010**.....

**Mr. E. Masupye**  
**P.O.Box 1140**  
**FAUNA PARK**  
**0787**

**RE: EVALUATION OF EXTEMPORANEOUS COMPOUNDING IN**  
**POLOKWANE HOSPITAL PHARMACIES**

- Your request to conduct outreach as above has been received.
- Permission granted by HOD is noted.
- PMHC has no objection in allowing the incumbent to conduct the research within the premises of the hospital.
- Research must be conducted in such a manner that:
  - a) It does not disrupt provision of service.
  - b) It does not expose patients to undue demands.
  - c) The PMHC Research and Ethics Committee is aware and monitors the process.
  - d) Research result must be used only for the purpose of the study.
- Permission shall be produced at any point when needed at the institution.

**Thank you.**




---

**Dr. Khoabane R.S.**  
**CEO, PMHC**

---

**Excellent Service Delivery**

POLOKWANE HOSPITAL CAMPUS  
DEPARTMENT OF HEALTH & SOCIAL DEVELOPMENT  
Cor. HOSPITAL & DORP STREET  
PRIVATE BAG X9316  
POLOKWANE  
0700  
TEL: (015) 287 5000  
FAX: (015) 297 2604



MANKWENG HOSPITAL CAMPUS  
DEPARTMENT OF HEALTH & SOCIAL DEVELOPMENT  
PRIVATE BAG X1117  
SOVENGA  
0727  
TEL: (015) 286 1000  
FAX: (015) 267 0206

**The heartland of Southern Africa - development is about people**

#### ANNEXURE 4: Letter of approval to conduct the study at the hospital



**LIMPOPO**  
PROVINCIAL GOVERNMENT  
REPUBLIC OF SOUTH AFRICA

### DEPARTMENT OF HEALTH AND SOCIAL DEVELOPMENT

Enquiries: Ramalivhana NJ/Malomane EL

Ref: 4/2/2

26 March, 2010

Mrs E Masupye

P.O.Box 1140

FAUNA PARK


0787

Dear Mrs E Masupye

#### **"Evaluation of extemporaneous compounding in Polokwane hospital pharmacies"**

Permission is hereby granted to Mrs E Masupye to conduct a study as mentioned above in Limpopo Province, South Africa

- The Department of Health and Social Development will expect a copy of the completed research for its own resource centre after completion of the study.
- The researcher is expected to avoid disrupting services in the course of his study
- The research results must be used only for the purpose of the study
- The Researcher/s should be prepared to assist in interpretation and implementation of the recommendations where possible
- The Institution management where the study is being conducted should be made aware of this,
- A copy of the permission letter can be forwarded to Management of the Institutions concerned

  
\_\_\_\_\_  
HEAD OF DEPARTMENT  
HEALTH AND SOCIAL DEVELOPMENT  
LIMPOPO PROVINCE

Private Bag X9302 Polokwane  
18 College Str., Polokwane 0700 • Tel: 015 293 6000 • Fax: 015 293 6211 • Website: <http://www.limpopo.gov.za>

***The heartland of southern Africa - development is about people***

## ANNEXURE 5: Data collection tool for pharmacists

### PHARMACISTS INTERVIEW INSTRUMENT

Name of hospital: \_\_\_\_\_

Code allocated to hospital: \_\_\_\_\_

#### 1. Demographic data

##### 1.1 Age in years

20 – 30	1
31 – 40	2
41 – 50	3
51 – 60	4
61 – 70	5

##### 1.2 Gender

Female	1
Male	2

##### 1.3 Race

1. Black	1
2. White	2
3. Indian	3
4. Coloured	4
5. Chinese	5
6. Other	6

1.4 In which category of personnel do you belong?

1. Chief pharmacist	1
2. Principal pharmacist	2
3. Senior pharmacist	3
4. Pharmacist	4
5. Pharmacy intern	5
6. Registered pharmacist assistant	6
7. Unregistered pharmacist assistant	7
8. Community service pharmacist	8
9. Pharmacy assistant basic	
10. Pharmacy assistant learner basic	

1.5 In which qualification category do you belong?

1. Doctorate	1
2. Masters	2
3. Bpharm	3
4. Diploma in Pharmacy	4
5. Other (specify)	5

## 2 Compounding skills

2.1 Do staff members receive training in compounding?

Yes	1
No	2

2.2 Which training **methods** are used for pharmacy staff in your hospital for compounding?

*(Tick the appropriate method applicable)*

1. On the job via personal practice	Yes	1	No	2
2. Formal lecture	Yes	1	No	2
3. Video	Yes	1	No	2
4. Supervision by experience	Yes	1	No	2
5. Training by external service providers	Yes	1	No	2
6. Other (specify)				

2.3 Which training **areas** are covered in your training? *(Choose the appropriate training areas)*

1. Sourcing or retrieving formulation	Yes	1	No	2
2. Use of references	Yes	1	No	2
3. Use of equipment in compounding, e.g. electronic balances, mortar and pestle, ointment slabs, etc	Yes	1	No	2
4. Labelling	Yes	1	No	2
5. Record keeping: compounding record	Yes	1	No	2
6. Record keeping: formulation record	Yes	1	No	2
7. Tests conducted	Yes	1	No	2
8. Quality assurance processes on, e.g. aseptic technique	Yes	1	No	2
9. Other (please specify)				



2.4 What compounding challenges do you encounter in your pharmacy?

1. No formulations	1
2. Calculations	2
3. Standard Operating Procedures not revised	3
4. Other (specify)	4

3. Compounding procedures

3.1 How often are the following listed records included in the documentation of this pharmacy?

	Never	Sometimes	Often	Always
1. Manufacturing batch records				
2. Compounding formulae and procedures				
3. A log of all compounded items				
4. Balance maintenance				
5. Standard Operating Procedures				

3.2 What **resources** do staff members use for obtaining formulations in compounding?

1. Published literature(specify)	1
2. Other hospitals	2
3. Other pharmacies e.g. retail	3
4. Personally developed/in-house formulations	4

#### 4 Establishment of expiry dates

4.1 How are expiry dates for compounded preparations established?

1. In-house stability testing	1
2. External contractor for stability testing	2
3. Recommendations from other hospitals pharmacies	3
4. Recommendations from pharmacies, e.g. retail	4
5. Personally established generalized expiry dates for various dosage forms	5
6. Other (specify	

4.2 Are the following available in your pharmacy?

	Yes	No
1. Compounding policies and procedures		
2. Electronic balances		
3. Proof of record of regular calibration of balances		
4. Proof of record of regular maintenance of balances		
5. Proof of record of maintenance of other manufacturing equipment		

4.3 If no, please specify how record is kept

--

4.4 What are the reasons for compounding in your pharmacy?

1. Allergy	1
2. Prescription drug not available	2
3. Unsuitable dosage form	3
4. Unsuitable route	4
5. Cost	5
6. Taste	6
7. Other (specify)	7

Thank you.

ANNEXURE 6: Data collection sheet for the compounded medicines

DATA COLLECTION SHEET  
  
NAME OF HOSPITAL  
CODE ALLOCATED

FREQUENCY

DATA COLLECTION SHEET  
FREQUENCY  
  
NAME OF HOSPITAL  
CODE ALLOCATED

Name of preparation & strength	Batch #	Date of preparation	Quantity	Dosage form	Expiry date	Shelf-life	Route of Administration	Ward setting	Preservatives	Reason for comp	Disease condition	Formulation problems if any	Class of Patient				
													Geriatrics	Neonates	Infants	Children	Adults
														0-27 days	28 days- 23 months	2-11yrs	
1								1	1								
2								2	2								
3								3	3								
4								4	4								
5								5	5								
6								6	6								
7								7	7								
8								8	8								
9								9	9								
10								10	10								
11								11	11								
12								12	12								
13								13	13								
14								14	14								
15								15	15								
16								16	16								
17								17	17								
18								18	18								
19								19	19								
20								20	20								

## **ANNEXURE 7: Consent form for the pharmacists**

### **Memo**

**From: E.M Masupye**

**To: The participant**

**Re: Invitation to participate in a study**

I, as a student in the Health Sciences, Pharmacy and Pharmacology Department, University of Kwa-Zulu Natal, Westville Campus, am involved in a study to evaluate the extemporaneous compounding in Polokwane hospital pharmacies.

The procedure to be followed in this study is to administer a questionnaire to willing participants in order to assess the frequency, extent, nature and information related to extemporaneous preparations. The study will identify the types of extemporaneously prepared products compounded in Polokwane hospital pharmacies, the most frequently prepared product in those hospitals and the demographic data of the pharmacy personnel.

I would like to invite you to participate in this research study. Please find attached a consent form. Participation is voluntary and you are free to withdraw from the study at any time. If at any stage you have queries or questions about the research, or would like to obtain more information about this study, please feel free to contact me and I will gladly answer your questions.

Yours sincerely

Masupye E.M

Tel: 015 268 2356/9

School of Pharmacy and Pharmacology

University of Kwa-Zulu Natal (Westville Campus)

P/Bag X4001

Durban

4000

## UNIVERSITY OF KWAZULU NATAL CONSENT FORM

**ANNEXURE 8: Map of the province (Mapsofworld.com)**

