ADDIS ABABA UNIVERSITY

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ASSESSMENT OF NON-STERILE PHARMACEUTICAL COMPOUNDING PRACTICES AMONG SELECTED COMMUNITY AND HOSPITAL PHARMACIES IN ADDIS ABABA, ETHIOPIA

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List of Acronyms

BUD:	Beyond-Use Date
FDA:	U.S. Food and Drug Administration
SOP:	Standard Operating Procedure
EFMHACA:	Ethiopia Food, Medicine and Health Care Administration and Control Authority
CD:	Compounded Drug
USP:	United States Pharmacopoeia
DACA:	Drug Administration and Control Authority
CSP:	Compounded Sterile Preparation
API:	Active Pharmaceutical Ingredient
SD:	Standard Deviation
WHO:	World Health Organization

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Abstract

Background: The drug products available in the market are mostly ready-made finished drug products. These drugs should be manufactured in pharmaceutical industries using the standard on Good Manufacturing Practice (GMP). But, it is a common practice to prepare topical preparations in compounding laboratories in premises like hospital pharmacies and community pharmacies in order to fulfill the special needs of individual patients. These preparations, like other finished drug products, should fulfill efficacy, safety, and quality parameters. This is achieved by adherence to the established standards that guide the preparation of compounded pharmaceutical preparations.

Objective: To assess the practices of non-sterile pharmaceutical compounding in selected community and hospital pharmacies in Addis Ababa.

Methods: A descriptive cross-sectional study supported by qualitative study was conducted to assess the practices of non-sterile pharmaceutical compounding in community and hospital pharmacies in Addis Ababa from April 1, 2016 to May 15, 2016. The study was done in 42 community pharmacies and 3 hospital pharmacies.

Results: The study revealed that the most commonly prescribed and compounded non-sterile pharmaceutical formulations in the community and hospital pharmacies in Addis Ababa were dermatological creams and ointments. Except for one community pharmacy, no community and hospital pharmacy provided on-the-job training to the pharmacy personnel involved in compounding. The compounding personnel in 41(97.6%) of the community and 2 of the hospital pharmacies were not familiar with the non-sterile pharmaceutical compounding laboratory standards developed by DACA in 2002.Twenty (47.6%) of the community pharmacies and 1 of the hospital pharmacies had no suitable place for compounding. All of the assessed hospital pharmacies had dedicated place for compounding and only authorized personnel is allowed in the specified room but 20 (47.6 %) of the community pharmacies had a compounding area with other works performed in that area. All of the hospital pharmacies and 39 (92.9%) of the community pharmacies had adequate potable water. The compounding area was maintained in a clean and sanitary condition in 25 (59.5 %) of the community pharmacies and all of the hospital pharmacies.

Standard operating procedures were not maintained in 41 (97.6%) of the community pharmacies and 1 of the hospital pharmacies. No community and hospital pharmacy created a master formulation record the first time before compounding new preparation. The equipment and materials required by the national regulatory authority for the extemporaneous preparation were not fulfilled in 18 (42.2%) of the community pharmacies and in 1 of the hospital pharmacies. Sixteen (38%) of the community pharmacies had no compounding record at all and 26 (62%) of the community pharmacies had compounding records which only contained the name and the strength of the compounded preparations. There were containers and closures that were not suitable for the preparation compounded in 18 (42.9%) of the community pharmacies and 1 of the hospital pharmacies.

Conclusions: The study revealed that**,** both the community and the hospital pharmacies did not fulfill most of the requirements set by the regulatory authority. However, the hospital pharmacies were found to be better than the community pharmacies in some of the requirements such as labeling of finished preparations, documentation, availability of equipments and compounding room dedication. As per the findings of this study, only one community pharmacy is practicing most of the standard requirements set for non-sterile pharmaceutical compounding. The major limiting factors for the implementation of the standard requirements set was identified to be lack of awareness on the standard set for non-sterile pharmaceutical compounding laboratories; the limited number of demands for the service; lack of on-the-job training and follow up from regulatory body and other stakeholders.

Recommendations: The non-sterile pharmaceutical compounding service has to be regulated and inspected strictly. The standards of good compounding laboratories developed by the regulatory authority should be cascaded and popularized to the professionals working in the community and hospital pharmacies. On-the-job training has to be given for the personnel involved in non-sterile pharmaceutical compounding. Further research should be done on the quality of non-sterile pharmaceutical compounding practices in other parts of the country.

Key words: Community pharmacy, hospital pharmacy, non-sterile pharmaceutical compounding Personnel qualification, compounding facility, equipment, documentation, quality control, Addis Ababa

1. Introduction

Pharmaceutical compounding is the combining, mixing, or altering of ingredients to provide a customized medication for an individual patient required by a licensed practitioner (USP, 2008; Zaid, 2011; Shaughnessy, 2012; Qureshi, *et al*., 2014).

The practice of pharmacy compounding can be traced back to ancient times with compounding pharmacies existing for thousands of years in some form. The Middle East purportedly has the first pharmacy in Baghdad in the 1st century A.D.; alchemy and compounding were used. Compounding pharmacies have been in America since the early 19th century (Timko and Crooker, 2014).

There is evidence that the hunter-gatherer societies and even ancient civilizations had some knowledge of the medicine properties of various plants, animals, molds and inorganic elements. Ancient civilizations found many uses for pharmaceutical compounding, including treating ill patients keeping the healthy well and for religious and cosmetics purposes. The first compounders extracted oils from plants and animals discovered poisons and antidotes, and prepared ointment for wounded patients. The earliest chemists studied various natural substances and their potential uses (Walls, *et al*., 2014). Traditionally, prescription medications were produced as compounded formulation by physicians themselves who mixed the medicine they prescribed for their patients. It was not until the late 19th century that the roles of doctor and pharmacist were distinguished (Baum, 2016).

Before mass production of medications becomes the mainstay, compounding was the only source of medicines and was a routine activity among pharmacists (Walls, *et al*., 2014). It was pivotal in establishing the pharmacy profession and was an important component of practice until the 1930s (Lau, *et al*., 2013). Pharmacy compounding declined in 1950s and 1960s with the increase in mass drug manufacturing (Roark, *et al*., 2014).

Traditionally, compounded drugs are made in response to an individual prescription from a licensed health provider in the context of a pharmacist's and health care provider's

professional relationship with a specific patient (Gudeman, *et al*., 2013). In the past few decades, however, the practices associated with pharmacy compounding have evolved. Large compounding pharmacies produce vast quantities of drugs that are copies of commercially available medications even though these drugs do not differ in any meaningful way from the commercial product they are mimicking (Mullarki, 2009).

In many countries nowadays, the activity of compounding is a complementary practice to the production of medicine in alternative amount and diversified dosage forms (liquid, semisolid, solid) in community pharmacy as well as hospital pharmacy (Dias, *et al*., 2013). The need for these compounded medicines differs among countries and is influenced by the availability of suitable dosage forms, and the requirements of specific patient populations (Lau, *et al*., 2013). For example, it accounts for approximately 10% of prescriptions dispensed annually in the United States. Pharmacy compounding is a vital service that helps many people and serves an important public health needs for the patients who cannot be treated with the FDA approved medications (Roark, *et al*., 2014).

Among the main therapeutic needs to be met by compounded products, there are allergies due to excipients contained in medicinal products manufactured by the pharmaceutical industry: hence, products will be compounded without allergy causing excipients (FDA, 2012, Sasich and Sukkari, 2008); orphan drugs: active ingredients that are developed specifically to treat rare medical conditions; medicines for clinical trials and placebo prepared in the hospital pharmacy; customize therapy like pain management therapy; medicines with stability issues; medicines awaiting authorization (Minghetti, *et al*., 2014).The other role includes, medicines for pediatric patients since the pharmaceutical industry does not often develop pediatric dose and dosage forms, to improve the patients' compliance or to obtain an additional or synergic effect (Tanninen, 2013).

Compounding has always been a basic part of pharmacy practice; today, it continues to be a rapidly growing area, and many pharmacists in all types of practices are becoming involved in compounding sterile and non-sterile preparations. Newly evolving dosage forms and therapeutic approaches suggest that compounding of pharmaceuticals and related products for individual patients will become more common in pharmacy practice

in the years ahead (Allen, 2015). For many years scientists and physicians have extolled the potential of personalized medicine. In the not-too-distant future prescription drugs will be tailor-made for an individual patient or for the groups of people with specific clinical needs. Today, pharmaceutical compounding is at the forefront of this movement towards personalized medicine. Patients are prescribed compounded drugs for their individual needs rather than receiving "one size fits all" fixed dose and mass produced drugs (Baum, 2016).

Pharmacy compounding provides pharmacists a unique opportunity to practice their time-honored profession. Although pharmacists should not hesitate to become involved in pharmacy compounding, they should be aware of the requirements for and uniqueness of formulating a specific drug product for a specific patient. It is an important component in providing pharmaceutical care. After all, without the pharmaceutical product there is no pharmaceutical care (Allen, 2015).

There are several general principles of pharmaceutical compounding that must be followed. Compounding ingredients must have the appropriate identity, purity and quality, and must be purchased from reliable sources and stored under proper storage conditions. All equipment must be clean maintained and used appropriately, the compounding environment must be suitable, and cross contamination must be prevented. Only authorized personnel are allowed in the immediate area where compounding is taking place. Processes must be reproducible, compounding conditions must be adequate for preventing errors, all aspects of compounding must be appropriately documented, and procedures and records must exist for correcting problems (USP, 2008; Milkiewicz, 2015).

There are two broad categories of compounded drugs: sterile preparations, also known as Compounded Sterile Preparations (CSPs) and non-sterile preparations. CSPs are higher risk products that are generally administered to patients via injection or infusion. Preparation of CSPs requires more expertise and more extensive safety measures (Levinson, 2015).

Sterile compounding requires specialized condition such as laminar air flow and access controlled clean rooms. This form of compounding is normally limited to manufacturing industries or institutions that have the appropriate facilities (Schultz, 2007).

Non-sterile preparations are lower risk products. Standards for producing non-sterile preparations are less stringent than those for CSPs (Levinson, 2015).

Most preparations compounded in a community pharmacy are categorized as non-sterile. These products usually include creams, ointments, lotions, mixtures, suspensions and solutions.

Non-sterile preparations are not required to be totally free from living organisms such as bacteria. It is however important to ensure that products are free from contaminants that may compromise the product quality (Schultz, 2007).

In the Ethiopian situation, DACA developed a standard for non-sterile pharmaceutical compounding laboratories in 2002 in order to systematize and enable pharmacy professionals prepare quality pharmaceutical products (DACA, 2002). But data on the state of compounding practices is lacking. The aim of this study is to fill these research gaps.

2. Statement of the problem

Compounding remains one of the highest risk preparative activities carried out in pharmacy as the risks of unlicensed medicines are combined with the inherent risks associated with the compounding of a formulation. There appears to be little consistency regarding the practice of compounding within and across countries and continents. Standardizing compounding practices and harmonizing formulations and information on stability would go a long way to guaranteeing the quality, safety and efficacy of compounded preparations (Nunn, 2011).

When compared to Good Manufacturing Practices (GMPs), the manufacturing standards required by FDA for commercial products, there are multiple recognized deficiencies inherent in extemporaneous formulation compounding (Mehta, *et al*., 2015).

Pharmacy compounded drugs have been associated with quality defects, infectious disease outbreaks and other adverse events which, in some cases, have involved patient deaths. In 2006, the FDA conducted a limited survey of compounded drugs. Of 36 samples tested by the FDA, 12 failed at least one quality test, with a failure rate of 33% (FDA, 2006; Sellers and Utian, 2012).

The potential safety risks for CDs include problems with potency (i.e., the dosage is inaccurate, either too strong or too weak), purity (e.g., the drug contains other chemicals that could be harmful), and contamination (the drug is contaminated with a bacteria, fungus, or virus). An inaccurate dose may present a risk of harm to the patient through a risk of toxicity (super-potent) or the risk of ineffective treatment (sub-potency) (Peques, 2006; Markey, 2012).

The global lack of documented and standardized formula 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 (Masupye, *et al.*, 2015). Since compounding preparations pose a high risk to patient safety and generally subject to low levels of quality assurance,

adherence to standards for compounding is necessary to ensure safe preparation of good quality products (Nunn, 2011).

3. Significance of the study

Compounded preparations, like other finished drug products, should fulfill efficacy, safety, and quality parameters. These are achieved by adherences to the established standards that guide the preparations of compounded pharmaceutical products (DACA, 2002).

Assessment of community and hospital pharmacies on adherence of good compounding practice is crucial to measure the status of non-sterile pharmaceutical compounding practices. Though there is EFMHACA regulation, data on the current state of the standard practices is lacking. This assessment will provide information to what level the community and hospital pharmacies in Addis Ababa are adhering to the non-sterile pharmaceutical compounding laboratories standards developed by the regulatory authority. The information gathered in this study could serve as an input to the regulatory body and stakeholders to strengthen and improve the performance of the facilities in producing safe, effective and quality compounded preparations. Besides, this research could help the community and hospital pharmacies to fill their gaps with better commitment.

4. Objectives of the study

4.1. General objective

To assess the practices of non-sterile pharmaceutical compounding in selected community and hospital pharmacies in Addis Ababa, Ethiopia.

4.2. Specific objectives

- To assess the practices of non-sterile pharmaceutical compounding in selected community pharmacies in Addis Ababa, Ethiopia.
- To assess the practices of non-sterile pharmaceutical compounding in selected hospital pharmacies in Addis Ababa, Ethiopia.
- To compare and contrast the practices of non-sterile pharmaceutical compounding in community and hospital pharmacies in Addis Ababa, Ethiopia.

5. Materials and methods

5.1. Study area, setting and period

The study was conducted in Addis Ababa, the capital city of Ethiopia. The city is divided into ten borough called sub cities and 116 woreda (lowest level administrative unit in the city). There are 896 health facilities (11 public hospitals, 94 public health centers, 38 private hospitals, 750 private specialty and medium clinics).

The study was conducted in selected community and hospital pharmacies in Addis Ababa which were engaged in non-sterile pharmaceutical compounding from April 1 to May 15, 2016.

5.2. Study design

A descriptive cross-sectional study design supported by a qualitative study was conducted to assess the practices of non-sterile pharmaceutical compounding in community and hospital pharmacies in Addis Ababa.

5.3. Population

5.3.1. Source population

All community and hospital pharmacies engaged in non-sterile pharmaceutical compounding and those personnel who were involved in compounding in the facilities in Addis Ababa.

5.3.2. Study population

The selected community and hospital pharmacies compounding section and the compounding personnel who were available and willing to participate in the study.

5.4. Sample size and sampling technique

There were 113 (5 public and 108 private) community pharmacies and 3 public hospital pharmacies engaged in non-sterile pharmaceutical compounding. The total sample size was calculated to be 45 facilities by using (WHO, 2015) Service Availability and Readiness Assessment (SARA) sample size determination formula.

$n = [[(z^2 * p * q) + ME^2] / [ME^2 + z^2 * p * q / N]]*d$

Where:

n = sample size

z = confidence level at 99% (2.58) ME = margin of error (15%)

p = the anticipated proportion of facilities which fulfill the non-sterile pharmaceutical compounding standard requirements (0.5).

q = 1-p =0.5

N = population size d= design effect =1

The community pharmacies were stratified based on ownership as private and Kenema pharmacies. Then the private community pharmacies were stratified again based on their location into 10 strata (sub-city) except for community pharmacies having branches. The private community pharmacies having branches were categorized into one stratum. After stratification a sample size was allocated for each stratum proportional to their population size (the number of community pharmacies engaged in non-sterile pharmaceutical compounding). Out of five Kenema pharmacies engaged in non-sterile pharmaceutical compounding three were selected randomly. On this basis, a total of 42 community pharmacies (39 private and 3 Kenema) were selected for the study. The distribution of the community pharmacies selected for the study is shown in table 5.1. All the three public hospital pharmacies have been assessed since there are no private hospital pharmacies engaged in non-sterile pharmaceutical compounding.

Table 5.1: The distribution and proportionate sampling of the community pharmacies engaged in non-sterile pharmaceutical compounding in Addis Ababa, 2016.

Sub-city/strata	**No of community pharmacies engaged in non-sterile compounding (N)**	**Samples taken(n)**
Gulele	6	2
Kolfe Keranio	15	5
Yeka	6	2
Bole	15	5
Lideta	6	2
Nifas Silk Lafto	12	4
Kirkos	11	4
Addis Ketema	12	4
Arada	10	4
Akaki Kaliti	6	3
Pharmacies having branches	9	4
Kenema Pharmacies	5	3
Total	**113**	**42**

5.5. Variables for the study

5.5.1. Independent variables

Socio demographic variables (age, sex, educational level, work experience).

Availability of qualified personnel, suitable compounding facilities, equipment, compounding procedures, compounding records and quality control processes.

5.5.2. Dependant variables

Infrastructural and service provision quality in non-sterile pharmaceutical compounding in community and hospital pharmacies.

5.6. Data collection tools

Data was collected by using structured observational checklists, self administered structured questionnaires and semi structured interview guide. The structured observational checklists were developed according to (USP, 2008; Allen, 2013; DACA, 2002) guidelines to assess the actual practices of non-sterile pharmaceutical compounding in community and hospital pharmacies in Addis Ababa.

The self administered structured questionnaires were used to assess socio-demographic characteristics of the respondents who participated in the study.

The semi structured interview guide has two parts. The first part was developed to assess the personnel qualification of the professional involved in compounding and the second part focuses on the detail compounding practices, challenges and opportunities for the implementation of standards developed by the regulatory authority for non-sterile pharmaceutical compounding in community and hospital pharmacies in Addis Ababa.

Pre-test was conducted in two community pharmacies which were not involved in the final study. Modification of the data collection tools according to Ethiopian situation was done before the actual data collection.

5.7. Operational definitions

Compounder: A professional authorized by the appropriate jurisdiction to perform compounding pursuant to a prescription or medication order by a licensed prescriber.

Manufacturing: The production, propagation, conversion, or processing of a drug or device either directly or indirectly, by extraction of the drug from substance of natural origin or by means of chemical or biological synthesis. Manufacturing may also include any packaging or repackaging of the substance(s) or labeling or relabeling of containers for resale by pharmacies, practitioners or other persons.

Suitable compounding area site : A compounding area site which is far from area or premises that can cause contamination to the raw materials, or finished products and equipments such as, bacteriological laboratories, kitchen, waste disposal site and other similar area.

Suitable container: A pharmaceutical container which is free from visible signs of dirt, crack or dust.

Active pharmaceutical ingredient (API): Any substance or mixture of substance intended to be used in the compounding of a drug preparation, thereby becoming the active ingredient in that preparation and furnishing pharmacological activity or other direct effect in the diagnosis, cure mitigation, treatment, or prevention of diseases in humans and animals or affecting the structure and function of the body.

Added substance: An ingredient that is necessary to compound a preparation but is not intended or expected to cause a pharmacologic response if administered alone in the amount or concentration contained in a single dose of the compounded preparation. The term is used synonymously with the term inactive ingredient, excipient, and pharmaceutical ingredient.

Beyond use date (BUD): The date after which compounded preparation should not to be used; determined from the date the preparation is compounded.

Expiry date: It is the point in time when the medication is no longer within an acceptable condition to be considered effective.

Hazardous drug: Any drug identified by at least one of the following six criteria: carcinogenicity, teratogenicity, or developmental toxicity, reproductive toxicity in humans ,organ toxicity at low dose in humans or animals, genotoxicity, new drug that mimic existing hazardous drug in structure or toxicity.

Preparation: A compounded drug dosage form or dietary supplement or device to which a compounder has introduced a drug. This term will be used to describe compounded formulation; the term product will be used to describe manufactured pharmaceutical dosage forms.

Community pharmacy: A community pharmacy is a health care facility that provides pharmaceutical service to the community and run by a registered pharmacist.

Hospital pharmacy: It is the organization or department of the hospital to manage the procurement, storage, preservation, packaging, sterilization, compounding, preparation, dispensing or distribution of medicines in the hospitals.

5.8. Ethical consideration

Ethical clearance was obtained from the Ethics Review Board of the School of Pharmacy, College of Health Sciences, Addis Ababa University. Permission was also obtained from the Addis Ababa city administration FMHACA and from the ten sub-cities. Information was provided to participants about the purpose of the study. They were also informed that participation is voluntary. Participants were also assured that the information they provide will be treated with strict confidentiality and neither their name nor the name of their institution will be mentioned in any report rather aggregated analysis of the data will be performed. Informed consent was obtained from all individuals participating in the study.

5.9. Data Quality Management

Data consistency and completeness was assured throughout the data collection, data entry and analysis by checking each questionnaire on the day of data collection. Validation of

data entry was done by cross checking the hard copy with the database, by doing exploratory analysis on frequency and cross tabulations.

5.10. Data analysis procedures

Completed questionnaires, were checked for completeness and accuracy on the data collection day. Data was entered to SPSS version 20.0 and cleaned and analysis of the data was done using descriptive statistics. The descriptive analysis included frequency tables and measures of central tendency of relevant variables.

6. Results

6.3. Quantitative findings

The study was done in 42 community pharmacies and 3 hospital pharmacies found in Addis Ababa, Ethiopia. Of the total 113 community pharmacies and 3 hospital pharmacies engaged in non–sterile pharmaceutical compounding, the 42 community pharmacies and 3 hospital pharmacies were assessed. The response rate was 100% as all of the selected community and hospital pharmacies gave the required information.

The study assessed the eight basic quality aspects of non-sterile pharmaceutical compounding, i.e. personnel qualification, compounding facility, procedures, equipments, documentation, handling and storage, containers and closures and quality control.

6.3.1.Compounding facilities

In this section seventeen requirements were assessed (Table 6.1). Though the compounding facility is the key for compounding practice 20 (47.6%) of the community pharmacies and 1 of the hospital pharmacies did not have suitable place for compounding. All of the assessed hospital pharmacies had dedicated place for compounding and only authorized personnel is allowed in the specified room but 20 (47.6 %) of the community pharmacies had a compounding area with other works performed in that area. Adequate potable water was available in 39 (92.9%) of the community pharmacies and all of the hospital pharmacies. The compounding area was clean in 25 (59.5%) of the community pharmacies and all of the hospital pharmacies. The space in the compounding room was not orderly arranged, there was no proper placement of equipment and materials to prevent mix-ups between ingredients, in-process materials, containers and finished preparations in the community pharmacies but the hospital pharmacies were well arranged.

Table 6.1: Non-sterile pharmaceutical compounding facility requirements fulfillment in selected community and hospital pharmacies in Addis Ababa, 2016

Requirements	Community pharmacy		Hospital pharmacy	
	Frequency (%) N = 42		Frequency N = 3	
	No	Yes	No	Yes
Suitability of the site of compounding area	20 (47.6)	22 (52.4)	1	2
Only authorized personnel allowed in the compounding area	20 (47.6)	22 (52.4)	0	3
For the type and amount of compounding done sufficient space availability(3x3 sq.m)	20 (47.6)	22 (52.4)	1	2
Good arrangement to prevent mix-up between ingredients	22 (52.4)	20 (47.6)	0	3
Good arrangement to prevent mix-up between containers	23 (54.8)	19 (45.2)	0	3
Good arrangement to prevent mix-up between labels	23 (54.8)	19 (45.2)	0	3
Good arrangement to prevent mix-up between in-process materials	23 (54.8)	19 (45.2)	0	3
Good arrangement to prevent mix-up between finished preparations	22 (52.2)	20 (47.6)	0	3
The space in the compounding room arranged to prevent cross contamination	21 (50)	21 (50)	0	3
The compounding area well lighted	19 (45.2)	23 (54.8)	0	3
The bulk storage area adequately arranged	23 (54.8)	19 (45.2)	0	3
Temperature monitoring done in the bulk storage area	40 (95.2)	2 (4.8)	2	1
Availability of adequate potable water in the compounding area	3 (7.1)	39 (92.9)	0	3
Availability of soap or detergent in the compounding area	5 (11.9)	37 (88.1)	0	3
The compounding area cleanliness	17 (40.5)	25 (59.5)	0	3
The bulk storage area cleanliness	17 (42.9)	25 (59.5)	0	3
Trash disposed of in timely manner	3 (7.1)	39 (92.9)	0	3

6.3.2. Compounding procedures

Standard operating procedures were prepared only in one community pharmacy and in two hospital pharmacies. No community and hospital pharmacy created a master formulation record the first time before compounding a new preparation. According to the respondents evaluation of the dose, safety, and intended use of the preparations for the patient was done only in 24 (57.1%) of the community and 2 of the hospital pharmacies. Even though all the information required in the record keeping was not fulfilled, 26 (62) % of the community pharmacies and all of the hospital pharmacies had a compounding record for each compounded preparations and the remaining community pharmacies had no compounding record at all (Table 6.2). There were 1 community and 2 hospital pharmacies which had adequate procedures and records for investigating and correcting failure or problems in compounding, testing, or in the preparation itself.

Table 6.2: Adherence to non-sterile pharmaceutical compounding procedures in selected community and hospital pharmacies in Addis Ababa, 2016

Requirements	Community pharmacy		Hospital pharmacy	
	Frequency (%) N = 42		Frequency N = 3	
	No	Yes	No	Yes
Evaluation of the dose, safety, and intended use of the preparations for the patient	18 (42.9)	24 (57.1)	1	2
Creation of a master formulation record the first time before compounding new preparations	42 (100)	0 (0)	3	0
The creation of the compounding record for each compounded preparations	16 (38)	26 (62)	0	3
Ingredients have been checked to confirm they have their expected identity and purity	41 (97.6)	1 (2.4)	3	0
Compounding conditions and procedures in place for preventing errors	41 (97.6)	1 (2.4)	1	2
Procedures and records exist for investigating and correcting failure or problems in compounding, testing, or in the preparation itself	41 (97.6)	1 (2.4)	1	2
Only one preparation at a time is compounded	0 (0)	42 (100)	0	3
Critical processes (weighing, measuring, and mixing) is verified so they will result in consistent preparations)	39 (92.9)	3 (7.1)	2	1
As appropriate the final completed preparation is assessed for weight	42 (100)	0 (0)	2	1
As appropriate the final completed preparation is assessed for mixing	9 (21.4)	33 (78.6)	1	2
As appropriate the final completed preparation is assessed for clarity	42 (100)	0 (0)	3	0
As appropriate the final completed preparation is assessed for odor	0 (0)	42 (100)	0	3
As appropriate the final completed preparation is assessed for color	0 (0)	42 (100)	0	3
As appropriate the final completed preparation is assessed for consistency	0 (0)	42 (100)	0	3
The finished preparation is appropriately packaged	1 (2.4)	41 (97.6)	0	3
The labeling on the finished preparation meets the labeling requirement	41 (97.6)	1 (2.4)	1	2
The preparation is dispensed to the patient or care giver with appropriate consultation	0 (0)	42 (100)	0	3

6.3.3. Compounding equipments

The equipments and materials required by the national regulatory authority were not generally fulfilled in 18 (42.9%) of the community pharmacies and in 1 of the hospital pharmacy. The equipments available were properly maintained and used in 25 (59.5%) of the community pharmacies and all of the hospital pharmacies (Table 6.3).Calibration of the weighing machine was only done in one community pharmacy.

Table 6.3: Availability and proper use of non-sterile pharmaceutical compounding equipment in selected community and hospital pharmacies in Addis Ababa, 2016

Requirements	**Community pharmacy**		**Hospital pharmacy**	
	Frequency (%) N = 42		**Frequency N = 3**	
	No	**Yes**	**No**	**Yes**
Availability of equipments and materials required by the national regulatory authority	18 (42.9)	24 (57.1)	1	2
All equipment maintained and used appropriately	17 (40.5)	25 (59.5)	0	3
All equipments of appropriate design such that the surfaces that contact pharmaceutical component, in process materials, or finished preparation are not reactive, additive or adsorptive	29 (69)	13 (31)	1	2
All equipment inspected for cleanliness and proper functioning prior to each use	4 (9.5)	38 (90.5)	0	3
All equipment thoroughly cleaned promptly, after use to avoid cross contamination	4 (9.5)	38 (90.5)	0	3
Calibration of equipments done	41 (97.6)	1 (2.4)	2	1
Disposable equipment or supplies used disposed of immediately	0 (0)	42 (100)	0	3

6.3.4. Compounding documentation

No pharmacy created a master formulation record the first time before compounding new preparations. There were no standard operating procedures for the preparations compounded in 41 (97.6%) of the community pharmacies and 1 of the hospital pharmacies (Table 6.4). A compounding record was maintained for the name and strength of the preparations compounded in 26 (62%) of the community pharmacies and all of the hospital pharmacies. But there was no documentation about the source and lot number of ingredients used, total number of dosage units compounded, master formulation record reference, compatibility and stability information, all the equipment used, containers used, sample labeling information, description of the finished preparation, storage requirement, assigned BUD, mixing instruction to include order of mixing, temperatures, duration of mixing and other pertinent factors for the preparation.

Name of the person compounding the preparation was documented only in 16 (38%) of the community pharmacies and all of the hospital pharmacies. A detailed compounding record for assigned internal identification number or the prescription number was maintained only in one community pharmacy and none of the hospital pharmacies.

Table 6.4: Documentation practices of non-sterile pharmaceutical compounding in selected community and hospital pharmacies in Addis Ababa, 2016

Requirements	**Community pharmacy**		**Hospital pharmacy**	
	Frequency (%) N = 42		**Frequency N = 3**	
	No	**Yes**	**No**	**Yes**
Compounding record maintained in the pharmacy	16 (38)	26 (62)	0	3
Standard operating procedure maintained in the pharmacy	41 (97.6)	1 (2.4)	1	2
A detailed compounding record maintained for name and strength of the preparation compounded	16 (38)	26 (62)	0	3
A detailed compounding record maintained for total number of dosage units compounded of the preparation compounded	32 (76.2)	10 (23.8)	2	1
A detailed compounding record maintained for the name of the person compounding the preparation compounded	26 (62)	16 (38)	0	3
A detailed compounding record maintained for date of compounding	17 (40.5)	25 (59.5)	0	3
A detailed compounding record maintained for assigned internal identification number or the prescription number of the preparation compounded	41 (97.6)	1 (2.4)	3	0
A detailed compounding record maintained for description of the final preparation of the preparation compounded	19 (45.2)	23 (54.8)	1	2

6.3.5. Component selection, handling, storage and labeling

Some ingredients which have no expiration date on the container were found in 39 (92.9%) of the community pharmacies and in 1 of hospital pharmacies. Also most of the community pharmacies had no SOP to assign conservative expiration date for substances without an expiration date assigned by the manufacturer or supplier.

The labeling on the finished preparations did not meet the labeling requirements in 41 (97.6%) of the community pharmacies and 1 of the hospital pharmacies .The information on the labels was also hand written in most of the community pharmacies.

The compounding personnel understand the difference between an expiration date and BUD in only 13 (69%) of the community pharmacies and 2 of the hospital pharmacies. The BUDs were not assigned according to the source of the active ingredients and the type of preparation in 38 (90.5%) of the community pharmacies and in one hospital pharmacy. In addition the assigned BUDs were not written on the label in 41 (97.6%) of the community pharmacies and 1 of the hospital pharmacies (Table 6.5). The labeling on the finished preparations did not meet the labeling requirements in 41 (97.6%) of the community pharmacies and 1 of the hospital pharmacies. The information on the labels was also hand written in most of the community pharmacies.

Table 6.5: Handling, storage and labeling practices of non-sterile pharmaceutical compounding in selected community and hospital pharmacies in Addis Ababa, 2016

	Community pharmacy		**Hospital pharmacy**	
Requirements	**Frequency (%) N = 42**		**Frequency N = 3**	
	No	**Yes**	**No**	**Yes**
The purity scale considered and in the purchasing of ingredients	11 (26.2)	31 (73.8)	0	3
All substances have a complete label, batch control number, and future expiration date on the container	39 (92.9)	3 (7.1)	1	2
For substances without an expiration date assigned by the manufacturer or supplier, the pharmacy have an SOP to assign conservative expiration date on the substances	42 (100)	0 (0)	3	0
When manufactured products are used for compounding all the other excipients in the product considered relative to the compounded preparation to be made	39 (92.9)	3 (7.1)	3	0
The compounding personnel understand the difference between an expiration date and BUD	13 (31)	29 (69)	1	2
Every formulation evaluated for incompatibilities and the potential for an ineffective or even potentially toxic preparation	22 (52.4)	20 (47.6)	1	2
Beyond use date assigned from the day of preparation	7 (16.7)	35 (83.3)	0	3
Preparations stored properly prior to dispensing based up on conditions up on which the BUD was assigned	9 (21.4)	33 (78.6)	0	3
Every preparation examined immediately after preparation and immediately prior to dispensing for any signs of instability	7 (16.7)	35 (83.3)	0	3
The BUD assigned according to the source of the active ingredient and the type of preparation	38 (90.5)	4 (9.5)	1	2
As appropriate, microbiological preservatives used	41 (97.6)	1 (2.4)	3	0
If not preserved instruction to refrigerate provided	4 (9.5)	38 (90.5)	0	3
BUDs placed on the label affixed to the prescription	41 (97.6)	1 (2.4)	1	2

6.3.6. Containers and closures

There were containers that were unsuitable in 18 (42.9%) of the community pharmacies and 1 of the hospital pharmacies. The containers and closures handled and stored to

prevent contamination in 27 (64.3%) of the community pharmacies and 2 of the hospital pharmacies (Table 6.6).

Table 6.6: Availability and suitability of non-sterile pharmaceutical compounding drug preparation containers in selected community and hospital pharmacies in Addis Ababa, 2016

Requirements	**Community pharmacy**		**Hospital pharmacy**	
	Frequency (%) N = 42		**Frequency N = 3**	
	No	**Yes**		
The compounding personnel awareness of standards for glass and plastic containers	16 (38.1)	26 (61.9)	1	2
Suitability of the containers used for the compounded preparations in the pharmacy	18 (42.9)	24 (57.1)	1	2
Containers and closures stored off the floor	16 (38.1)	26 (61.9)	1	2
The containers and closures handled and stored to prevent contamination	15 (35.7)	27 (64.3)	1	2

6.3.7.Quality control

This study revealed that the non-sterile pharmaceutical compounding practices in community and hospital pharmacies were not subjected to any quality control procedures beyond visual inspection of ingredients and the finished preparations.

6.3.8.Personnel qualification

The compounding personnel in 41(97.6%) of the community pharmacies and 2 of the hospital pharmacies were not familiar with the compounding laboratory standard developed by DACA in 2002. The compounding personnel were able to define the terms related to compounding such as, preparation, API, added substance, compounder, and

others. A significant number of participated compounding personnel (16) in the community and 1 in the hospital pharmacies were not aware of the advantages and disadvantages of glass and plastic containers. On- the- job training on the basics of non-sterile pharmaceutical compounding and specific to the preparations that were compounded in their pharmacy was given in only one of the community pharmacies and none of the hospital pharmacies. All of the assessed community and hospital pharmacies were inspected by their respective sub-city and Addis Ababa city administration FMHACA. But the inspection never focused on the compounding service.

6.3.9. Socio-demographic characteristics of respondents

Self administered structured questionnaires were filled by 45 of the compounding personnel of the studied community and hospital pharmacies. All of the respondents were pharmacists. Thirty three (73.3%) were male. The mean age was 35.8 years (SD=8.77).Thirteen (28.9%) were owners of the pharmacy and the others 32 were employed. Twenty-seven (60%) were graduated from governmental universities and 18(40%) were from private colleges. Majority of the respondents (62.2%) have a work experiences ranging from1-10 years. Most of the personnel (77.7%) have a longest time area of prior experience in community and hospital pharmacies (Table 6.7).

Table 6.7. Socio-demographic characteristics of respondents in selected community and hospital pharmacies in Addis Ababa, 2016

Variables	Category	N (%)
Sex		
	Male	33(73.3)
	Female	12(26.9)
Age		
	20-30	18(40)
	31-40	12(26.7)
	41-50	12(26.7)
	>50	3 (6.6)
Institution graduated		
	Governmental universities	27(60)
	Private colleges	18(40)
Years of work experience		
	1-5	15(33.3)
	6-10	13(28.9)
	11-15	7(15.6)
	16-20	2(4.4)
	21-25	4(8.9)
	>25	4(8.9)

Table 6.7 continued

Variables	Category	N (%)
Years working in the present pharmacy		
	1-5	33 (73.3)
	6-10	11 (24.5)
	>10	1 (2.2)
Longest time area of prior experience		
	Community pharmacy	23 (51.1)
	Hospital pharmacy	12 (26.7)
	Pharmaceutical industry	2 (4.4)
	Pharmaceutical wholesale	4 (8.9)
	Regulatory	3 (6.7)
	Teaching	1 (2.2)

6.3.10. Aggregate analysis of quantitative results

A total of 118 non-sterile pharmaceutical compounding requirements were assessed. The mean, range and SD of the assessed requirement fulfillment in the studied community and hospital pharmacies are shown in Table 6.8 and 6.9 respectively.

Table 6.8: Aggregated analysis of quantitative findings of non-sterile pharmaceutical compounding practices in selected community pharmacies in Addis Ababa, 2016

N=42						
Variables	**Number of requirements assessed**	**Number of requirements fulfilled**				
		Range	**Minimum**	**Maximum**	**Mean**	**SD**
Personnel qualification	15	5.00	8.00	13.00	9.09	0.759
Compounding facilities	17	16.00	0.00	16.00	8.66	5.58
Compounding procedure	20	8.00	7.00	15.00	9.80	1.50
Compounding equipment	8	6.00	1.00	7.00	4.07	1.47
Compounding documentation	30	10.00	0.00	10.00	3.76	2.98
Compounding storage and handling	15	10.00	1.00	11.00	6.52	2.03
Drug container and closure	4	4.00	0.00	4.00	2.45	1.67
Quality control	9	2.00	0.00	2.00	0.095	0.37
Overall practice	**118**	**55.00**	**21.00**	**76.00**	**44.47**	**12.6**

Table 6.9: Aggregated analysis of quantitative findings of non-sterile pharmaceutical compounding practices in selected hospital pharmacies in Addis Ababa, 2016

N=3						
Variables	**Number of requirements assessed**	**Number of requirements fulfilled**				
		Range	**Minimum**	**Maximum**	**Mean**	**SD**
Personnel qualification	15	3.00	9.00	12.00	10.33	1.52
Compounding facility	17	3.00	13.00	16.00	14.66	1.52
Compounding procedure	20	5.00	10.00	15.00	12.33	2.51
Compounding equipment	8	3.00	4.00	7.00	5.66	1.52
Compounding documentation	30	4.00	5.00	9.00	7.33	2.08
Compounding storage and handling	15	1.00	8.00	9.00	8.66	0.57
Drug container and closure	4	4.00	0.00	4.00	2.66	2.30
Quality control	9	0.00	0.00	0.00	0.00	0.00
Overall practice	**118**	**21.00**	**51.00**	**72.00**	**61.66**	**10.50**

6.3.11. Level category of the assessed community and hospital pharmacies

Since the community and hospital pharmacies did not fulfill most of the requirements set for each variable, the facilities were categorized into two, based on their performance on the requirements set for the purpose of this study, i.e. facilities which fulfill 50% standards requirements of the checklist used and those that fail to fulfill at least the 50% level. Table 6.10 shows the frequency (percentage) of the assessed community and hospital pharmacies fulfilling 50% and above standards requirements of each variable.

Table 6.10: Frequency (percentage) of facilities achieving 50% and above standards requirements of the checklist used in selected community and hospital pharmacies in Addis Ababa, 2016

S.no	**Variables**	**Community pharmacy N= 42**		**Hospital pharmacy N = 3**
		Frequency	**Percentage (%)**	**Frequency**
1	Personnel qualification	42	100	3
2	Compounding facilities	21	50	3
3	Compounding procedure	13	30.9	2
4	Compounding equipment	16	30	2
5	Compounding documentation	0	0	0
6	Storage and handling	15	35.7	3
7	Containers and closures	22	52.3	2
8	Quality control	0	0	0

As shown in Table 6.10 all of the community and hospital pharmacies were able to fulfill the 50% level personnel qualification requirements but most of the community pharmacies did not fulfill 50 % level of compounding equipment and procedure. No community and hospital pharmacy fulfilled this level requirement of documentation. The 50% level handling and storage requirements were fulfilled in all of the hospital pharmacies but not in the community pharmacies.

6.4. Qualitative findings

6.4.1. Findings of the in depth-interview

According to the respondents the most commonly prescribed and compounded formulations in the community and hospital pharmacies in Addis Ababa were dermatological creams and ointments. These include topical corticosteroids, hydroquinone, salicylic acid, sulfur, lactic acid, benzoic acid, resorcinol, coal tar, vioform, aluminium chloride, trichloroacetic acid and urea preparations. And these preparations are mainly compounded for psoriasis, fungal infections, cosmetics allergies, acne vulgaris and warts.

Most of the compounding personnel asserted that vioform, lactic acid, coal tar and resorcinol API are not available sustainably in the market.

Opinion on the availability of equipments and materials

Most of the respondents agreed that the equipments and materials they are using currently are not adequate for the work they were performing in their pharmacy. But two of the respondents said: *"I knew that I did not fulfill all the equipments and materials required by the regulatory authority but I did not see the importance of those equipments and materials since we are compounding very simple preparations in our pharmacy."*

Opinion on educational background of pharmacists

Most compounding personnel said that even though the education they received in school is important it has to be enhanced by on-the-job trainings. Some pharmacists said:

"Eventhough the education we have received in school gave us the basic knowledge about compounding, confidence and skill come from experience, so on-the-job training has to be given by experienced professionals."

The other respondents said: *"The education given in school regarding compounding does not address specific preparations. But here, individualized/specialist based/ prescriptions are compounded. Hence, there is a need to update the undergraduate pharmaceutical compounding course content based on the practical needs."*

Opinion on legislation

Most respondents said: *"In the current regulation, little attention is given for this service but pharmaceutical compounding is the basic part of pharmacy practice hence, the educational institutions as well as the regulatory authority should give due emphasis."*

One respondent mentioned that: *"I think capacity building is more important than inspection. Currently community pharmacies are considered as business organizations, there are no encouragements from the government, no one will focus on building our capacity but we are the first contact to the community often before the physician."*

One pharmacist gave a different opinion: *"I don't think that compounding has to be done in all of the community pharmacies; rather one or two compounding centers have to be established with properly trained personnel, adequate equipment and suitable compounding area."*

The other pharmacists said: I think pharmaceutical compounding should not be compulsory to community pharmacies. The main concern should be the quality of non-sterile pharmaceutical compounding service given to the community and technical support should be provided to the community pharmacies engaged in pharmaceutical compounding.

Opinion on Limiting factors for non-sterile pharmaceutical compounding

The limiting factors mentioned for the implementation of good non-sterile pharmaceutical compounding practices were, there are a limited number of demands for this service: hence the owners of the pharmacies are not encouraged to invest in the facility and equipment of compounding. The compounding rooms were prepared since it was a requirement of the standard for establishing a community pharmacy in the previous regulation.

Most pharmacists said:*"We just prepared this room since it was a requirement for establishing a community pharmacy, we will be very happy to use this room for other purposes since there are a few numbers of prescriptions coming for compounding*."

The other limiting factor they mentioned was that awareness was not created about the standard set by the regulatory authority so most of the compounding pharmacies were not informed and hence they are not trying to implement it. In addition on-the-job trainings were not given by compounding facilities or other stakeholders for the personnel involved in compounding.

7. Discussion

This study attempted to assess the quality of non-sterile pharmaceutical compounding service in selected community and hospital pharmacies in Addis Ababa.

In doing so, it measured the eight basic quality aspects of non-sterile pharmaceutical compounding practices which are personnel qualification, compounding facility, equipments, procedures, documentation, storage and handling, containers and closures, and quality control processes. It employed both quantitative and qualitative methods to describe the practice of non-sterile pharmaceutical compounding in the studied community and hospital pharmacies.

It was found that the most commonly prescribed and compounded formulations in the community and hospital pharmacies in Addis Ababa were dermatological creams and ointments. These include topical corticosteroids, hydroquinone, salicylic acid, sulfur, lactic acid, benzoic acid, resorcinol, coal tar, vioform, aluminium chloride, trichloroacetic acid and urea preparations. As per the findings of this study, the most common dermatological drug indications were psoriasis, fungal infections, cosmetics allergies, acne vulgaris and warts.

All of the assessed community and hospital pharmacies were inspected by their respective sub-city and Addis Ababa city administration FMHACA. But this inspection was not specific to the pharmaceutical compounding practices. An interesting result found in this study is 41 (97.6%) of the personnel involved in compounding in community pharmacies and 2 in the hospital pharmacies were not familiar with the non-sterile pharmaceutical compounding laboratory standard developed by DACA, in 2002. This indicates that the regulatory authority did not use the standard in the inspection of the community and the hospital pharmacies. The standard requirements had to be put into checklist to create awareness among the personnel working in the area and this had to be used as the golden criteria to measure the performance of the pharmacies in non-sterile pharmaceutical compounding practices.

According to Nemec, *et al*.,(2016),in modern health care system compounding pharmacies meet special patient care needs and the role of compounding pharmacies

continues to expand so pharmacist require hands-on training to be competent in the area. But in this study, except for one community pharmacy, no pharmacy provided on-the -job training about the basics of non-sterile pharmaceutical compounding and specifically to the products that were compounded in their pharmacy. And in the rest of the community and the hospital pharmacies skill transfer was done by simple observation of what their seniors did.

According to (Saudi Food & Drug Authority, 2010), all personnel involved in compounding, packaging, and dispensing of compounded preparations shall be properly trained for the type of compounding conducted and it is the responsibility of the pharmacist to ensure that a training program has been implemented and that it is ongoing.

All training activities must be thoroughly documented and may be incorporated into the employees personnel file. The employee must be continually monitored by the compounder as the compounder is solely responsible for the finished compounded preparation (Allen, 2012).

Regarding the compounding facility 20 (47.6%) of the community pharmacies and 1 of the hospital pharmacies had no suitable place for compounding. In addition 20 (47.6%) of the community pharmacies and 1 of the hospital pharmacies had no sufficient space for compounding. The reason for this is that, even though the community pharmacies had a designated place for compounding, in some of the pharmacies the compounding room was used as storage for pharmaceuticals and as office for the personnel working in the pharmacies.

The compounding area shall be clean, sanitary, and orderly and of sufficient space to perform the compounding activity involved; premises shall permit effective cleaning of all surfaces (DACA, 2002).However, in the current study, the compounding area was maintained in a clean and sanitary condition in only 25 (59.5 %) of the community and all of the hospital pharmacies. The space in the compounding room had to be arranged with the proper placement of equipment and materials to prevent mix-up between ingredients, in process materials, containers and labels but most of the community pharmacies 23 (54.8%) were not arranged well. Only 21 (50%) of the community

pharmacies were properly arranged to prevent cross contamination. Nineteen (45.2%) of the community pharmacies had no well lighted compounding area but this requirement is fulfilled in all of the hospital pharmacies. Proper temperature monitoring was done only in one community and one hospital pharmacy. Trash was disposed of in a timely manner in 39 (92.9%) of the community and all of the hospital pharmacies. Adequate potable water was used in 39 (92.9%) of the community and all of the hospital pharmacies. Trash disposal and adequacy of potable water were found to be better relative to other standard requirements of non-sterile pharmaceutical compounding laboratories of DACA (2002).

Concerning the compounding processes, none of the compounding pharmacies created a master formulation record the first time before compounding a new preparation. This is in consistent with the DACA (2002) standard requirements for non-sterile pharmaceutical compounding laboratories of community and hospital pharmacies. A master formulation record must be created before compounding a new preparation for each compounded preparation. This record should be followed every time the preparation is made, and record must be completed every time the preparation is made. Standard operating procedures were not maintained in 41 (97.6%) of the community pharmacies and 1 of the hospital pharmacies. This is in contradiction to DACA (2002) standard requirements for good non-sterile pharmaceutical compounding laboratories of community and hospital pharmacies. The pharmacy must have SOPs for the facility, equipment, personnel, preparation, packaging, and storage of compounded preparations to ensure accountability, accuracy, quality, safety and uniformity in compounding. Only SOPs that are actually implemented should be available in the compounding area. SOPs can be numbered and categorized according to any method suitable for the pharmacy (Allen, 2012).

According to the respondents evaluation of the dose, safety, and intended use of the preparations for the patient was only done in 24 (57.1%) of the community and 2 of the hospital pharmacies. The pharmacy personnel in some of the community pharmacies and in one hospital pharmacy said since the prescribed doses are individualized (not standardized), it is difficult to evaluate the dose and intended use of the preparations prescribed to the patients. Hence, they simply compound what was ordered in the prescription. The dose, the intended use, and the safety of the preparation must be

evaluated in terms of the chemical and physical properties of the components, the dosage form, the therapeutic appropriateness, the route of administration, and any legal limitations (Milkiewicz, 2015).

Only one preparation was compounded at a time, the preparation was dispensed to the patient or care giver with appropriate consultation in all of the community and hospital pharmacies. According to the respondents the final preparation was only assessed for color, odor, and mixing in most of the community and hospital pharmacies. The final preparation must be assessed using factors such as, color, weight, consistency etc, and this must be recorded on the compounding record. The preparation must be packaged appropriately. The labeling should include "this is a compounded preparation" (Milkiewicz, 2015).

The equipment and utensils required by the national regulatory authority for extemporaneous preparation (analytical balance, mortar and pestle, hot water bath, hot plate, spatula, ointment tile, wash bottle, funnel (glass or poly ethylene), beaker, graduated cylinders and glass rod) were not fulfilled in 18 (42.2%) of the community pharmacies and in 1 of the hospital pharmacy. In this regard, the hospital pharmacies were more equipped and the equipments and materials were maintained in a clean and sanitary condition than the community pharmacies. In addition, only one type of mortar and pestle was available for staining and non-staining materials in 29 (69%) of the community pharmacies. The available equipments were properly used in 25 (59.5 %) of the community pharmacies and all of the hospital pharmacies. Besides, calibration of the weighing machine used was only done in one community and one hospital pharmacy. All equipments were inspected for cleanliness and proper functioning prior to each use in 38 (90.5%) of the community pharmacies and in all of the hospital pharmacies. The equipment or utensils used for compounding of a drug product shall be of appropriate design and capacity. The equipment shall be cleaned and sanitized prior to use to prevent contamination that may affect the safety or quality of compounded preparations. Equipment used in compounding shall be routinely inspected, calibrated as necessary, and checked to ensure proper performance; immediately prior to initiation of

compounding operations, the equipment shall be inspected by the compounder to determine its suitability for use (USP, 2008).

Sixteen (38%) of the community pharmacies had no compounding record at all. Eventhough all the required information was not contained, all of the hospital pharmacies had a compounding record for the preparations compounded. And 26 (62%) of the community pharmacies had a compounding records which only contained the name and the strength of the compounded preparations. None of the community and hospital pharmacies had a compounding record for the source and lot number of ingredients used, total number of dosage units compounded, master formulation record reference, all the necessary calculations, the compatibility and stability information, the equipments and containers used, sample labeling information, storage requirement, assigned BUD, mixing instruction to include order of mixing, temperatures, duration of mixing and other pertinent factors for the preparation. This makes identification of the preparation compounded difficult. Hence, product recalling, adverse drug reaction and product quality problems monitoring would be complex. The compounding record should contain documentation of the name and strength of the compounded preparation, the formulation record reference for the preparation, and the sources and lot number of ingredients. It should also include information on the total number of dosage units compounded, the name of the person who prepared the preparation and the name of the compounder who approved the preparation, the date of preparation, the assigned internal identification number or the prescription number and an assigned BUD (Zaid, *et al*., 2011).

Date of compounding was recorded only in 25 (59.5%) of the community pharmacies and all of the hospital pharmacies. Name of the person compounding the preparation was documented in 16 (38%) of the community pharmacies and all of the hospital pharmacies. Documentation of the person compounding the preparation is important since the personnel are solely responsible for the preparation he/she was compounding. A detailed compounding record for assigned internal identification number or the prescription number was maintained only in one community pharmacy and in none of the hospital pharmacies. This is inconsistent with the DACA (2002) standard requirements for non-sterile pharmaceutical compounding laboratories.

Both the community and hospital pharmacies had some ingredients without expiration dates on the containers and most of the community pharmacies had no SOP to assign conservative expiration date for substances without an expiration dates provided by the manufacturer or supplier. This indicates that the safety, efficacy, and quality of the ingredients used were not guaranteed. The regulatory authority has to control such practices.

Based on the observation of this study the labeling information was hand written in most of the community pharmacies and the labels had no BUD and control number in 41 (97.6%) of the community pharmacies and 1 of the hospital pharmacies. The label on dispensed medicines is one of the most important sources of information available to the patients. It facilitates the safe and effective use of medicines by the patients. Non-compliance to good labeling practice is a risk factor for medication error. The BUDs were not also assigned according to the source of the active ingredient and the type of preparations in most of the community pharmacies and one of the hospital pharmacies. The labels of the compounded preparations should contain beyond use date and it has to be assigned according to the source of the active ingredients of the preparations. When a manufactured product is used as an active ingredient in a compounded preparation, the product expiry date cannot be used solely to assign a BUD. BUD should be assigned conservatively, while using professional judgment based on pharmaceutical education and experience (USP, 2008).

The study revealed that there were containers and closures that were not suitable for the preparation compounded in 18 (42.9%) of the community pharmacies and 1 of the hospital pharmacies. This includes the usage of transparent containers instead of amber color containers for products requiring this type of containers; some of the containers had visible signs of dirt and dust that the possibility of contamination is very high. The containers and closures were handled and stored to prevent contamination in 27 (64.3%) of the community pharmacies and 2 of the hospital pharmacies. The containers and closures have an impact on the stability of the preparations. Plastic containers can contribute to decreased stability of some compounded products (Ensom, *et al*., 2007). Phenolic compounds are used in various dermatological compounded preparations. The

stability of phenol was dependant on the packaging material. After twelve weeks storage of an aqueous phenol solution in glass 100.9% phenol remained (due to some water evaporation the original phenol concentration increased a bit), in rigid PVC 99.8% and polyethylene (common plastic) 99.1%.Thus plastic bottles are inappropriate for the packaging of aqueous solution of phenolic compounds (Bakker, *et al.*, 2012).This highlights the importance of using the correct container for non-sterile pharmaceutical compounded preparations. Compounders are encouraged to review relevant resources before compounding and packaging non-sterile pharmaceutical preparations (Kawano, Certina, 2012). But in this study a significant number of compounding personnel (38.1%) in the community pharmacies 1 in the hospital pharmacies were not able to explain the advantages and disadvantages of glass and plastic containers.

The compounding personnel in most of the community and hospital pharmacies claimed that, even if it was not documented, quality control procedures such as, visual inspection of ingredients and finished preparations were performed. But, it was mentioned that there was no master formulation record the first time before compounding a new preparation. Hence, it is difficult to crosscheck whether the finished preparation complied with the master formulation record and investigate the discrepancy and to take appropriate corrective action. The safety, quality, and performance of compounded preparations depend on correct ingredients and calculations, accurate and precise measurements, appropriate formulation condition and procedures, and prudent pharmaceutical judgment. As a final check the compounder shall review each procedure in the compounding process. To ensure accuracy and completeness the compounder shall observe the finished preparations to ensure that it appears as expected and shall investigate any discrepancies and take appropriate corrective action before the prescription is dispensed to the patients (USP, 2008).

All of the interviewed compounding personnel have some knowledge of defining the terms related to compounding. But 41 (97.6%) of the compounding personnel in the community pharmacies and 2 in the hospital pharmacies were not familiar with the standard requirements for non-sterile pharmaceutical compounding laboratories developed by DACA in 2002. They explained that the inspection done to their

pharmacies did not pay any attention to compounding service given and also to this standard. Besides, this service has been regulated as optional, i.e. any pharmacy which is interested can compound. Most of the personnel only knew the EFMHACA requirements for establishing a community pharmacy since compounding service was compulsory for establishing a community pharmacy in the previous regulations. The pharmacists also asserted that, community and hospital pharmacy inspection has to focus on the quality of service given in compounding practice in addition to room dedication for compounding.

Regarding training only one community pharmacy gave on-the-job training to the staff involved in compounding. Most of the interviewed pharmacists in the community and hospital pharmacies said that the education they received in school is required to acquire knowledge but, it is not sufficient to develop skill in every aspect.

As per the opinion of the interviewed compounding personnel the limiting factor mentioned for the implementation of good non-sterile pharmaceutical compounding practices were, there are a limited number of demands for this service hence: the owners of the pharmacies were not encouraged to invest in the facility and equipment of compounding that, most community pharmacies preferred to use the compounding room for other purposes such as storage of pharmaceuticals; awareness was not created about the standard requirements set for non-sterile compounding laboratories of community and hospital pharmacies; lack of training and follow-up from the regulatory authority and other stakeholders. They also mentioned that educational institutions should put their effort in development of qualified professionals since pharmaceutical compounding is the basic part of pharmacy practices.

One pharmacist suggested that one or two compounding center be established with trained personnel, adequate equipment, and suitable compounding area rather than compounding in every community pharmacy.

8. Conclusions and recommendations

The study revealed both the community and the hospital pharmacies did not fulfill most of the requirements set by the regulatory authority. However, hospital pharmacies were found to be better than the community pharmacies in some of the requirements such as labeling, documentation, equipment qualification and compounding room dedication. As per the findings of this study, only one community pharmacy is practicing most of the standard requirements set for non-sterile pharmaceutical compounding. The major limiting factors mentioned for the implementation of non-sterile pharmaceutical compounding standard requirements were identified to be lack of awareness on the standards set for compounding laboratories; the limited number of demands for the service; lack of training and follow-up from the regulatory body and other stakeholders.

As multidimensional as they are, these problems require concerted efforts by the regulatory authority, educational institutions, and professional associations to improve the quality of non-sterile pharmaceutical compounding practices in community and hospital pharmacies.

Based on the findings of the study, the following recommendations are forwarded.

- The compounding service has to be regulated and inspected with due emphasis.
- The standards of non-sterile pharmaceutical compounding laboratories developed by the regulatory authority should be cascaded and popularized to the professionals working in the community and hospital pharmacies.
- Continuous, regular and standards based supervision and technical support should be provided to the pharmacies engaged in non-sterile pharmaceutical compounding.
- The regulatory body should have a clear documentation of the community and hospital pharmacies which are engaged in non-sterile pharmaceutical compounding.
- Educational institutions should put strong effort in the development of qualified professionals.

- On-the- job training has to be given for the personnel involved in non-sterile pharmaceutical compounding.
- Further research should be done on the quality of non-sterile pharmaceutical compounding practice in other parts of the country.

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Annexes

Annex 1 Information sheet

Good day! My name is Sofia Seid. I am conducting a survey on the "Assessment of non-sterile pharmaceutical compounding practices among selected community and hospital Pharmacies found in Addis Ababa "for the partial fulfillment of master's thesis program in Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Science, Addis Ababa University. I am here to gather relevant information regarding the research with a view to assess the current status of non sterile pharmaceutical compounding practices and to put forward recommendations on how to improve the standard practices of this service.

Your facility was selected randomly to participate in this study. I will be asking you questions about non sterile pharmaceutical compounding practice in your facility. The Information you provide will be treated with strict confidentiality and neither your name nor the name of your institution will be indicated in any report. Rather the facility will be identified by a code and aggregate analysis of data will be performed without making reference to particular individual or institution.

You may refuse to answer any question or choose to stop the interview at any time. However, we hope you will answer the questions, which will benefit the services you provide and the nation.

Information collected during this study may be used by policy makers, NGOs or researchers for quality improvement or conducting further studies on compounding practices.

If there are questions for which someone else is most appropriate to provide the information, we would appreciate it if you could provide us address or introduce us to that person to help us collect that information.

Thank you for your kind support

Annex 2 Consent form

1. I have read the information sheet that explains the reasons for the study that I am being asked to participate in.
2. I had the opportunity to ask questions and all the questions I had about the study have been answered.
3. I clearly understand what is being asked of me if I agree to participate in this study.
4. I also know that I have the right to leave the study at any time if I do not want to continue.
5. I am aware that all the information that I give will be kept with confidentiality.
6. I agree to take part in this study.

NAME OF KEY INFORMANT (in capital letters)	----------
NAME OF INSTITUTION	----------
SIGNATURE	----------
DATE (in DD/MM/YYYY)	----------

Annex 3 Checklists for observation of the non-sterile pharmaceutical compounding practices in selected community and hospital pharmacies in Addis Ababa, 2016

Addis Ababa University

School of pharmacy

Department of pharmaceutics and social pharmacy

Facility name----------

Facility code----------

Type of facility
Hospital pharmacy ----------1 Community pharmacy ----------2
Location of facility (Sub-City) _____

May I begin the observation?

YES. 1

NO. . . . . ..…2 STOP →

Section 1. Compounding Facilities

S.no.	Item	Yes	No	Comment
1.1	Is the compounding area suitable for its intended purpose?			
1.2	Are only authorized personnel allowed in the immediate area where compounding occurs?			
1.3	For the type and amount of compounding done, is sufficient space available?			
1.4	Is the space orderly arranged with proper placement of equipment and materials to prevent mix-ups between			
1.4.1	Ingredients?			
1.4.2	Containers?			
1.4.3	Labels?			
1.4.4	In process materials?			
1.4.5	Finished preparation?			
1.5	Is the space arranged to prevent cross contamination?			
1.6	Is the compounding area well lighted?			
1.7	Is the bulk storage area adequately arranged?			
1.8	Is the proper temperature monitoring done in the bulk storage area?			

S.no	Item	yes	No	Comment
1.9	In the compounding area, are the following available?			
1.9.1	Adequate potable water?			
1.9.2	Soap or detergent?			
1.10	Is the compounding area clean?			
1.11	Is the bulk storage area clean?			
1.12	Is trash disposed of in timely manner?			

Section 2. Compounding Process

S.no.	Item	Yes	No	Comment
2.1	Evaluation of the dose, safety, and intended use of the preparations for the patient?			
2.2	Creation of a master formulation record the first time before compounding new preparations?			
2.3	Also the creation of the compounding record for each compounded preparation?			
2.4	Ingredients have been checked to confirm they have their expected identity and purity?			
2.5	Compounding is done in clean and sanitized, dedicated area?			
2.6	Are compounding conditions and procedures in place for preventing errors?			
2.7	Do adequate procedures and records exist for investigating and correcting failure or problems in compounding, testing, or in the preparation itself?			
2.8	Only one preparation at a time is compounded?			

S.no.	Item	Yes	No	Comment
2.9	Compounding personnel maintain good hand hygiene and wear clean and appropriate clothing for the compounding being performed and also is appropriate for their protection?			
2.10	Critical processes (weighing, measuring, and mixing is verified so they will result in consistent preparations?			
2.11	. As appropriate the final completed preparation is assessed for			
2.11.1	. Weight?			
2.11.2	. Mixing?			
2.11.3	. Clarity?			
2.11.4	. Odor?			
2.11.5	. Color?			
2.11.6	. Consistency?			
2.12	. The finished preparation is appropriately packaged?			
2.13	. The labeling on the finished preparation meets the labeling requirement?			
2.14	. The master formulation record and the compounding record have been reviewed by the compounder to ensure it is error free?			
2.15	. The preparation is dispensed to the patient or care giver with appropriate consultation?			

Section 3. Compounding Equipment

S.no.	Item	Yes	No	Comment
3.1	Is the equipment and materials required by the national regulatory authority fulfilled?			
3.2	Is all equipment clean, properly maintained and appropriately used?			
3.3	Are all equipments of appropriate design such that the surfaces that contact pharmaceutical component, in process materials, or finished preparation are not reactive, additive or adsorptive?			
3.4	Is all equipment inspected for cleanliness and proper functioning prior to each use?			
3.5	Is all equipment thoroughly cleaned promptly, after use to avoid cross contamination?			
3.6	Is equipment used for allergenic ingredients appropriately handled, cleaned, and stored immediately after use?			
3.7	Are all items of equipment calibrated at appropriate intervals?			
3.8	If disposable equipment or supplies are used, are they disposed of immediately?			

Section 4. Compounding documentation

S.no.	Item	Yes	No	Comment
4.1	Is documentation available that compounding is only done by individuals that are appropriately trained and validated?			
4.2	Is documentation available that all ingredients used have their expected identity and purity?			
4.3	Is documentation available that all preparations are packaged and labeled appropriately?			
4.4	Is the record- keeping requirements followed?			
4.6	Are the available records maintained in the pharmacy?			
4.7	Master formulation record?			
4.8	Compounding record?			
4.9	SOPs?			
	Master formulation record			
4.10	Is detailed formulation record maintained for each compounded preparation?			
4.10.1	Name strength and dosage forms?			
4.10.2	All necessary calculations?			
4.10.3	All ingredients and their quantities?			

4.10.4	Compatibility and stability information?			
4.10.5	Equipment used for the preparation?			
4.10.6	Mixing instruction to include order of mixing, temperatures, duration of mixing and other pertinent factors?			
4.10.7	Assigned BUD?			
4.10.8	Container used?			
4.10.9	Sample labeling information?			
4.10.10	Description of the finished preparation?			
4.10.11	Storage requirement?			
4.10.12	Quality control procedures?			

S.no.	Item	Yes	No	Comment
	Compounding records			
4.11	Is a detailed compounding record maintained for each compounded preparation?			
4.11.1	Name and strength of the preparation?			
411.2	Master formulation record reference?			
4.11.3	Source and lot number of ingredients?			
4.11.4	Total number of dosage units compounded?			
4.11.5	Name of person compounding the preparation?			
4.11.6	Date of compounding?			
4.11.7	Assigned internal identification number or the prescription number?			
4.11.8	Description of the final preparation?			
4.11.9	Assigned BUD?			
	Standard operating procedures/SOPs			
4.12	Is every significant procedure in the compounding pharmacy addressed by a well written and implemented SOP?			

Section 5. Component selection, handling, storage and labeling

S.no.	Item	yes	No	Comment
5.1	Is the purity scale considered and appropriately used in the purchasing of ingredients?			
5.2	Are drug substance purchased from a registered facility?			
5.3	Do all substances have a complete label, batch control number, and future expiration date on container?			
5.4	For substances without an expiration date assigned by the manufacturer or supplier, does the pharmacy have an SOP to assign conservative expiration date on the substances and is it followed?			
5.5	When manufactured products are used for compounding do the labels contain a batch control number and a future expiration date?			
5.6	When manufactured products are used for compounding are all the other excipients in the product considered relative to the compounded preparation to be made?			
5.7	Does the compounding personnel understand the difference between an expiration date and beyond use date (BUD)?			

S.no.	Item	Yes	No	Comment
5.8	Is every formulation evaluated for incompatibilities and the potential for an ineffective or even potentially toxic preparation?			
5.9	Are beyond use date assigned from the day of preparation?			
5.10	Are preparations stored properly prior to dispensing based up on conditions up on which the BUD was assigned?			
5.11	Is every preparation examined immediately after preparation and immediately prior to dispensing for any signs of instability?			
5.12	Is the BUD assigned according to the source of the active ingredient and the type of preparation?			
5.13	As appropriate, are microbiological preservatives used?			
5.14	If not are instructions to refrigerate provided?			
5.15	Are BUDs placed on the label affixed to the prescription?			

Section 6. Packaging and drug preparation containers

S.no.	Item	Yes	No	Comment
6.1	Is the pharmacy aware of standards for glass and plastic containers?			
6.2	Are suitable containers used for the compounded preparations in the pharmacy?			
6.3	Are containers and closures stored off the floor?			
6.4	Are the containers and closures handled and stored to prevent contamination?			

Section 7. Quality control

S.no.	Item	Requirements	Yes	No	Comment
7.1	Does the compounder review each procedure in the compounding processes?				
7.2	Does the compounder observe the finished preparation to ensure it appears as expected in the master formulation record?				
7.3	If the finished preparation does not appear as it should, does the compounder investigate the discrepancy and take appropriate corrective action before the prescription is dispensed to the patient?				
7.4	Does the pharmacy regularly test preparations for physical and chemical characteristics?				
7.5	Are the routine compounding procedures for batch preparation completed and verified according to				
7.5.1	Written procedures?				
7.5.2	Calculation correct?				
7.5.3	Weighing and measuring done correctly?				
7.5.4	Order of mixing correct?				
7.5.5	Compounding techniques performed correctly?				

Annex 4. Self administered structured questionnaires for the assessment of socio-demographic characteristics of the respondents in selected community and hospital pharmacies in Addis Ababa, 2016.

Addis Ababa University

School of pharmacy

Department of pharmaceutics and social pharmacy

Facility name----------

Facility code----------

Type of facility Hospital pharmacy ----------1 Community pharmacy----------2
Location of facility (Sub-City) _____

Are you ready to fill these questionnaires?

YES. 1

NO. . . . . 2 STOP →

Please reply to the following questionnaires by choosing from the categories given.

1. Gender ☐ Male ☐ Female

2. Age ☐ 20-30 ☐ 31-40 ☐ 41-50 ☐ >50

3. Highest education level completed

☐ Msc ☐ B.Pharm ☐ Druggist ☐ Others

4. From which institutions you are graduated?

Universities ☐ Governmental ☐ Private

College ☐ Governmental ☐ private

5. Years of experiences after graduation? ☐ 1-5 ☐ 6-10 ☐ 11-15 ☐ 16-20 ☐ 21-25 ☐ >25

6. How long you have been working in this pharmacy? ☐ 1-5 ☐ 6-10 ☐ >25

7. What is your longest time area of prior experience?

☐ Community pharmacy ☐ Pharmaceutical whole sale

☐ Hospital pharmacy ☐ Regulatory

☐ Pharmaceutical industry ☐ Teaching ☐ Others

8. Are you the owner of the pharmacy? ☐ Yes ☐ No

Annex 5. Guides for interview with the participated compounding personnel in selected community and hospital pharmacies in Addis Ababa, 2016

Addis Ababa University

School of pharmacy

Department of pharmaceutics and social pharmacy

Facility name----------

Facility code----------

Type of facility
Hospital pharmacy ----------.1 Community pharmacy----------2
. Location of facility (Sub-City) _____

May I begin the interview?

YES. 1

NO. . . . . ….2 STOP →

Part 1.Questions to assess the personnel qualification of the professionals involved in non-sterile compounding in selected community and hospital pharmacy in Addis Ababa, 2016

1. Are you familiar with the non- sterile pharmaceutical compounding laboratory standards developed by DACA in 2002?
2. In your opinion what are the requirements to compound preparations of acceptable strength quality and purity?
3. Could you please define what a "preparation "is?
4. Could you please define what a "compounder "is?
5. What is the difference between "compounding "and "manufacturing"?
6. Could you please define what an "active pharmaceutical ingredient "is?
7. Could you please define what added substance "is?
8. Are all compounded prescriptions dispensed pursuant to a prescriptions from a valid licensed prescriber?
9. Do you have SOPs that govern your daily activities?
10. Is there a training program in place for all involved in compounding?
11. Are all training activities documented?
12. Are compounding personnel prevented from compounding until they have been adequately trained and evaluated?
13. Are all compounding personnel evaluated at least annually?
14. What is the advantage and disadvantage of glass and plastic containers?
15. Does your pharmacy inspected by Addis Ababa city administration /sub city FMHACA?

Part 2. Questions to assesses the detail compounding practices in selected community and hospital pharmacies in Addis Ababa, 2016

1. Which kinds of formulations and APIs are compounded frequently in your pharmacy?
2. Which kinds of APIs you need have availability problem in the market?
3. Based on the prescribed indications which kinds of morbidity are most common in A.A?

4. Do you think that the current equipments and facility you are working with are adequate for the works you perform?
5. How do you assess the education you received in school making you capable of compounding non- sterile pharmaceutical preparations?
6. In your opinion, what are the hindrance factors for the implementation of good non-sterile pharmaceutical compounding laboratory standards?
7. What policy and legislative changes do you suggest to enable your pharmacy perform better in non-sterile pharmaceutical compounding service?
8. Is there anything you would like to add?