



Extemporaneous Compounding Practice for Dermatologic Preparations in Ethiopian Public Hospitals: Regulatory Requirements and Quality Concerns

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Abstract: Extemporaneous compounding is among the key hospital pharmacy services that promotes pharmaceutical care. It is a long-standing practice in dermatology for patients who need custom-made drug products. The practice of dermatologic compounding practice in Ethiopian public hospitals is found at the beginning and very few hospitals have started the practice so far. This research communication aimed at examining Ethiopian public hospitals' extemporaneous compounding practice for dermatologicals with emphasis on regulatory requirement and quality control activities. To benefit patients from these products, good compounding practice should be obeyed in line with the expansion of the service. Gaps have been observed in the facilities with regard to quality assurance system and compliance with the country's regulatory requirements. This implies a need to take appropriate and timely actions by the responsible stakeholders and expand the service in the country by fulfilling the regulatory requirement.

Keywords: compounding, dermatologic, extemporaneous, regulatory, quality, hospitals

Introduction

Drug compounding is as old as the practice of pharmacy and it was employed for the majority of prescriptions and accounts for about 80% of all the prescriptions until the 1950s since mass production of modern drug products began.^{1,2}

Compounding service, the art and science of creating personalized medicines, tries to find solutions for patients with special needs (eg, infants, children, the elderly) when the intended medicines are not commercially available.^{3–5} The United States Pharmacopeia (USP) has defined non-sterile compounding as combining, admixing, diluting, pooling, reconstituting, or otherwise altering a drug or bulk drug substance to create a non-sterile medication.⁶

In the history of dermatology, extemporaneous compounding holds a cherished place when commercial drugs were not available.⁵ For about 40 years, the compounding practice had been declining due to the emergence of mass production of pharmaceuticals. The practice was revived again in the 1990s though its contribution was not similar to that observed in the early 19's. Compounding is still a key component of pharmacy practice and a valuable therapeutic service, particularly in dermatology.^{1,2}

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Compounding pharmacists fill the important gap of customized medicines' availability that pharmaceutical manufacturers fail to produce. There are many reasons to practice dermatology compounding. The main reason is the need to provide products that are not easily available in the market. This allows opportunities to treat rare diseases or target specific aspects of a common disease. Combining two or more active ingredients into one product is the other reason for the practice. This will enhance patient convenience and save costs.⁵

Extemporaneous compounding has been kept as a viable option for dermatologists to treat skin diseases with topical medications. A typical reference mentioned that up to 5 compounded medications were prescribed by a dermatologist daily.⁷ Extemporaneous compounding is one of the required competencies of practice for pharmacists in many countries.⁸ Hospital pharmacies are among the areas where extemporaneous compounding is practiced.

Overview of the Dermatologic Compounding Practice in Ethiopian Public Hospitals

The pharmacy service areas in the majority of the country's public hospitals have been mainly concerned with the clinical pharmacy service, drug supply management, drug information, and dispensing services. According to the 2019/2020 report of Health Sector Transformation Plan I performance, nationally there are 353 functional hospitals in the country. As per the information obtained from the Ministry of Health-Ethiopia, there are only 17 public hospitals in the country that have established dermatologic compounding services as of November 2020 in which about 30% of them are located in the capital Addis Ababa. It is observed that more than one-third of public hospitals in the city have started the service which may be due to the concentration of a relatively large number of dermatologists in the city compared with other regions of the country.

Following the opening of the dermatology specialty training program for physicians in different higher educational institutions of the country, the number of graduating dermatologists seems slowly increasing recently. The assignment of dermatologists in various public hospitals has led to the starting of the extemporaneous compounding service in such health facilities. In recent times, healthcare providers and patients in the country linked to compounded dermatologic preparations are increasing.

Compounding is among the key hospital pharmacy services as clearly stated in the Ethiopian Hospital Services Transformation Guidelines.⁹ It promotes pharmaceutical care and alleviates drug shortage problems. The practice of dermatologic extemporaneous compounding should be implemented in hospitals by complying with the standards and maintaining the quality of products. There are some general principles for the compounding of non-sterile pharmaceutical preparations that must be respected and applied. The principles encompass, among the others, ingredients, premises for compounding and storage, equipment, sanitation and hygiene, quality control, and documentation. Most of the public hospitals in the country have dedicated premises for compounding service though there are issues about the sufficiency of room spaces and their construction suitability for cleaning. The major limitation of the practice observed in the majority of hospitals is the lack of pharmaceutical-grade ingredients and they are using analytical grade raw materials instead. Additionally, most facilities have faced a lack of standard and specific references for following a step-by-step procedure during the compounding of various dermatologic formulations. So far, all hospitals were compounding formulations by referring to some general books and based on experiential sharing from pharmacy personnel in other facilities. The preparation and dissemination of a non-sterile compounding guideline by the Ministry of Health in 2020 may lead compounders to the preparation procedures.¹⁰

These public hospitals have been compounding dermatological products based on prescriptions for identified individual patients but not in bulk preparation. But, some facilities additionally compounded anticipated products (ie, in advance of patient need) for some cases before receiving requests. Compounding of dermatologic preparations in the facilities is a good start to meet specific individual needs. But, such preparations should be done as per the regulatory requirements to deliver quality products to customers and make them maximally benefitted from the products. Though an overall assessment of the dermatologic extemporaneous compounding service in the country is lacking, it is shown, from personal observations and communication with the Ministry of Health-Ethiopia, that creams and ointments are the most commonly compounded dermatologic products in public hospitals. A study done in some hospitals found in Addis Ababa had also reported the same.¹¹

As a general, the pharmaceuticals' compounding and manufacturing practice in the hospital settings was an almost forgotten area of pharmacy practice in the country and found at an infancy stage. Recently, some attention is given to this service by the Ministry of Health-Ethiopia and considered as one initiative. A technical working group has been established to facilitate the implementation of this service in public hospitals, among which dermatological preparations are one. Despite the role of the dermatologic compounding service in public hospitals, there are concerns about regulatory and quality issues. So, the current perspectives focus on the views of public hospitals' dermatologic compounding services concerning the regulatory requirements and their quality.

Regulatory Framework

The drug regulatory authorities are expected to have inspection schedules for compounding facilities based on the potential risks and other conditions of compounded medicines.¹² Unlike commercial drug products that have undergone a premarket review for safety, effectiveness, and quality, and are manufactured in inspected facilities, compounding of extemporaneous preparations in health facilities usually does not pass through these processes in Ethiopia.

Extemporaneously compounded non-sterile products are not eligible for the exemptions of regulatory assessment. Despite this, the majority of public hospitals found in the country have started the practice without undergoing pre-assessment and having permission license from the Ethiopian Food and Drug Authority (EFDA) to do so.

Compounding of non-sterile pharmaceutical products is expected to be practiced as per the good compounding principles.⁶ For this, a standard for the establishment and practice of non-sterile pharmaceutical compounding laboratories was published in 2002 by the former Drug Administration and Control Authority of Ethiopia (DACA) which is now called EFDA.¹³ It stated the general requirements for firms to provide the compounding services that incorporate the premise, the environment, personnel, equipment, starting materials, documentation, packaging, and labeling.

As a general regulatory oversight, it looks that EFDA has ignored the practice of non-sterile drug compounding practice in public hospitals given its small-scale production, low risk, and individualized nature of the preparation. Unlike the public hospitals, community pharmacies providing non-sterile compounding services are inspected

regularly by the authority. Most hospitals have started the service with the technical and other supports obtained from the Ministry of Health-Ethiopia that does not have a regulatory role for the service. The lack of inspection of such compounding facilities at the initial stage as well as periodically may influence the quality of the compounded products. Despite its low-risk category nature according to EFDA¹⁴ the extemporaneous products should satisfy the regulatory requirements concerning professionals' qualification, good compounding practice, quality control activities, sanitation and hygienic practices, and documentation. Hence, there should be an inspection of hospitals to know their status and fulfillment of the minimum standards for compounding non-sterile preparations.^{6,13}

A study done in Addis Ababa revealed that lack of awareness on the standard set for non-sterile pharmaceutical compounding laboratories was among the reasons mentioned by the hospitals for their poor adherence to the regulatory requirements.¹¹ This reflected on the need for sensitization for pharmacy professionals about the regulatory requirements and regular follow-up from the regulatory body. There is also an assumption by the hospitals and the regulatory firm that the compounded drug products are subject to a lower regulatory standard than EFDA-approved commercial drugs.

Currently, extemporaneously compounded drug products obtained from community pharmacies and few public hospitals in the country are dispensed for the increasing number of patients for their dermatological conditions. Failing to implement the regulatory procedures on these facilities may have negative consequences on the treatment outcome of compounded dermatologicals. In the absence of strong regulatory measures, the establishment and the delivery of compounding services in the public hospitals will continue as observed now and other upcoming facilities will follow the same way.

The majority of public hospitals have started the service on premises that are not appropriate for the purpose as specified in the guideline.¹³ Other requirements including personnel, documentation, equipment, quality controls, and others are not fulfilled or practiced as required in the facilities.

As a regulatory authority, there is a need to confirm that the appropriate professionals are assigned for the compounding practice that follows the ethical standards and prepared dermatologicals as per the minimum standard set by EFDA. To acquire the required skills and

become proficient in the practice, the need for additional training in the art of compounding is recommended.¹⁵

Though simple compounding practice by using an established formula is one of the required competencies for all first-degree pharmacists in Ethiopia and others,¹⁶ additional training on basic components, processes and quality control activities is essential as a continuous professional development. For this, establishing compounding training centers in the country is recommended to equip professionals further with the required knowledge and skills. Unlike the case in other places, a specific license is not required for pharmacists to offer compounding services in the country. This licensure requirement should be changed after making training centers existed.

The current practice of compounding in hospitals indicated the need for a clear policy stating the regulatory requirement. Additionally, the need for a mandatory license to start a compounding center in hospitals, as practiced for community pharmacies and other small-scale manufacturers, should be clarified to the hospitals. Hence, pharmacy professionals, physicians, and healthcare facilities will have an awareness and basic understanding of the country's regulatory requirements on compounding practice. This can be done by the Ministry of Health or other responsible stakeholders. The EFDA should exercise its enforcing regulatory role in all health facility pharmacies. An increased effort to regulate the compounding practice is necessary as the practice is found to be expanding slowly in the country's public hospitals.

Quality Concerns

While the importance of extemporaneous compounding of dermatologicals is well established,^{2,5,17,18} the benefits of the products to patients are obtained provided that they are well prepared and found to be fit for their purposes.

When an approved commercial drug product is not appropriate for patients, eg, due to allergy, compounded drugs can serve an important role. However, they may also pose a higher risk to patients than the approved drugs if they are not prepared in such a way to meet the quality standard. Overdoses and exposure to contaminants are among the risks resulted from compounded drugs with poor quality.¹²

From the compounded products that may not follow the regulatory requirements, several quality concerns may arise that can lead to unpredictable effectiveness and potential toxicities.^{5,19–21} For compounded dermatological products containing active drug substances, acceptable

grade compounding ingredients (pharmaceutical grade) are recommended to be used as a starting material to obtain quality products leading to optimum results as indicated elsewhere.^{8,22} Quality of compounded products can also be guaranteed by considering the conditions under which the pharmacy professionals are performing the practice which otherwise may introduce the risk of contamination.⁵ The other conditions that are not usually considered are the dispensing containers and storage conditions. The design of compounded medicine dispensing containers may affect the stability of some light-sensitive and oxidizable products. This may happen when wide mouth jars are used for dispensing compounded preparations containing ingredient/s from a closed metal tube. With this aspect, it is observed that the majority of hospitals are found to use wide-mouth containers. In some facilities, the containers are not tightly fitted with closures for the dispensing of compounded ointments which may affect the stability of some products. The stability problem of the preparations may not be observed by the compounders since the products are given immediately to the patients for home use. Moreover, there are no recall mechanisms for products showing stability problems or reporting of such conditions by patients when occurred.

Unlike the bulk manufactured drug products, compounded prescriptions do not require comprehensive quality testing activities like potency, purity, and stability.^{16,23,24} But, there is a need for an overall quality assurance system that minimizes some potential risks associated with compounded medications which include sub potency, super potency, and contamination.^{1,25} Well-trained personnel and availability of standard operating procedures are among the others the practice demand.⁸ The compounding personnel should have a clear understanding of the physicochemical properties of ingredients as they may degrade when exposed to water or heat and may interact with other excipients used in the compounding process.^{4,16} This adequate knowledge can be obtained when relevant references are made available in the facilities and appropriate training is given to the professionals and operators.

Good personal hygiene and sanitation have a role in minimizing the contamination of products during compounding and protecting the operators from potential chemical hazards. With this regard, the emphasis given by the hospitals is not satisfactory. This behavior can be improved when the appropriate documentation is ready and follow-up is implemented. Hence, written or

electronic documentation should be maintained to demonstrate the compounding practice's compliance with the requirements.^{6,13}

Though stringent quality assurance protocol is not required for compounding of dermatologicals, the minimum requirements with premise, environment, raw ingredients, equipment, personnel, and documentation should be fulfilled. One of the quality issues raised on the compounding health facilities is the quality of raw ingredients used in the preparation. Pharmaceutical grade ingredients are rarely used due to their unavailability from the local market as the facilities explained. Such use of lower grade ingredients may compromise the treatments' outcomes and even may cause risks to the patients like exposure to toxic chemicals. The implementation of regular inspection of the facilities by the EFDA may make the facilities give emphasis and search for these ingredients. Additionally, the local chemical suppliers will have a market guarantee to import these products and avail for the compounding facilities.

The extemporaneously compounded dermatologicals are generally not self-evaluated for the quality parameters. Raw ingredients and finished products do not undergo evaluation for quality aspects like purity, particle size, viscosity, potency, stability, and other attributes that are appropriate to demonstrate products' performance. Without such evaluations of products for relevant quality parameters, some dosage forms or products may become unsafe or ineffective. Such concerns of quality raised on the compounding of extemporaneous preparations have been also a global issue as uniform standards were lacking.²⁶

Generally, the quality assurance program for the hospital compounding practice can result from the active involvement of multi-stakeholders including hospitals, the regulatory body, the Ministry of Health, and academic institutions.

Conclusion and Recommendations

The extemporaneous compounding practice for dermatologic preparations in Ethiopian public hospitals is being implemented without inspection of the service by the regulatory body of the country. Such lack of inspection may make other public hospitals start the service without complying with critical requirements.

It is necessary to conduct nationwide compounding practice assessments on public hospitals to know their status for the regulatory requirements and testing of

sample products for some quality parameters. This will provide evidence-based documents for the responsible bodies especially for EFDA to take timely mitigating measures and prevention of risks to the users. Moreover, there should be an awareness creation program by EFDA for facilities on the regulatory requirements during pharmaceutical compounding services. This will avoid the assumption of no permission needed to launch this service in health facilities.

Since, nowadays, compounding is considered as an integral part of the modern healthcare system of the country, its requirements should be given due attention by the regulatory authority. This will enforce health facilities to follow the requirements and maintain the quality of compounded products. Hence, the EFDA should devise an inspection program to evaluate the adequacy of the compounding process and the quality control activities in such facilities. On-the-job training should be devised by the Ministry of Health-Ethiopia and delivered to compounding personnel on good compounding practice principles and overall quality assurance of compounded dermatological products.

Generally, the current compounding practice status for dermatologicals in the public hospitals indicated the need for increased efforts on the regulation of the practice and quality assurance programs by the facilities.

Relevance and Future Studies

Such insight has pointed out the problems in the practice of compounding dermatologic preparations for stakeholders to implement the regulatory requirement after the inspection process. Other interested bodies can further assess the reasons for the lack of such preservice inspection and later follow up. This perspective may also draw the interest for others to conduct a nationwide assessment of public hospitals to know the status of dermatologicals compounding practice and identify the challenges for quality assurance and reason for failing to comply with the regulatory requirement.

Disclosure

The authors declare no conflicts of interest in this work.

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