



# Extemporaneous Compounding: Prevalence, Risks and Quality Assurance

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## ABSTRACT

Extemporaneously compounded products are designed for an individual patient based on a licensed physician's prescription in response to an identified need. Compounding provides medications for unique medical needs for which commercially manufactured products are unavailable. Compounding practice includes activities such as formulating, mixing, or repackaging of products. Extemporaneous preparations are not licensed by Drug Regulatory Authorities and hence, are not evaluated for quality, efficacy and stability. Also, adverse event reporting is not mandatory for these products. The need for extemporaneous preparations is precipitated by lack of commercially available products for all the medicines and dosage forms that are required by patients. Products intended for topical and pediatric use are the majority. Extemporaneous preparations are generally considered as high-risk products. Common risks of compounded products include calculation errors, microbial contamination, therapeutic failure and adverse reactions. To reduce the risks, Drug Regulatory Authorities have developed guidelines that describe the minimum standards to be followed when preparing for extemporaneous compounding to ensure product quality and fitness. Comprehensive assessment is performed to justify the need for these products. The preparation process should comply with all the Good Manufacturing Practices including design of compounding areas. Pharmacists performing compounding activities require appropriate knowledge, skills and competence to undertake the task. The ingredients used in compounding are subject to pharmacopeial quality standard and should be sourced from approved vendors. The final compounded product in some countries is controlled as stipulated in components standard. Extemporaneous compounding remains an important part of pharmacy practice. Comprehensive risk assessment, adherence to the prescribed manufacturing practices and use of national formularies are necessary for quality assurance of these preparations.

**Keywords:** Extemporaneous, Compounding, Quality, Efficacy



## INTRODUCTION

The art of extemporaneous compounding remains the cornerstone of patient-centered care within the complex landscape of modern pharmaceutical practice. This practice which has its roots in the age-old tradition of manufacturing tailored medications, addresses the unique therapeutic needs of individual patients that often is unmet by commercial formulations (Krause, 2009). As the healthcare industry continues to evolve, the relevance of extemporaneous compounding has surged, fueled by its capacity to bridge the gap between standardized drug regimens and the personalized requirements of diverse patient populations (Falconer & Steadman, 2017). Pharmaceutical compounding refers to the process of combining or modification of drug ingredients to produce medications for patient specific needs (Food and Drug Administration [FDA], 2021). Extemporaneous preparation refers to a therapeutic product compounded in community or hospital pharmacies for an individual patient according to the order of a licensed prescriber in the absence of a commercially registered option (Council of Europe, 2018; Pharmacy Board of Australia, 2015; "Pharmaceutical compounding - nonsterile preparations," 2014). The compounded product is issued to the patient or the authorized prescriber.

Historically, compounding was the basis of pharmacy (Camilleri et al., 2015) till mid 1900s when the pharmaceutical industry began to manufacture dosage forms and the need for extemporaneous preparation diminished. Seemingly, it has transformed over time into a specialized practice due to the advent of mass-produced pharmaceuticals. Notable though, the industry does not manufacture all the medicines and dosage forms that are required by patients. Consequently, a renewed recognition of its importance has emerged in recent years, fueled by factors such as: the need to adjust formulation strength (Carvalho & Almeida, 2022), to exclude an excipient (Carvalho & Almeida, 2022), the rise of rare diseases warranting orphan drugs such as sodium phenylbutyrate, primaquine phosphate and pyridoxal phosphate (Vanhoorne et al., 2019), problems drug instability (Belayneh & Tessema, 2021), change of route of administration and for patients who have difficulty swallowing solid dosage forms (Mohiuddin, 2019). The resurgence of extemporaneous compounding has brought to light not only its potential benefits but also the complex challenges it poses. Quality assurance, regulatory compliance, and patient safety have taken center stage in discussions surrounding this practice. As compounded medications bypass the arduous scrutiny applied to mass-manufactured drugs, concerns about consistency, stability, and potential risks (Mohiuddin, 2019) have emerged, necessitating a comprehensive evaluation of the landscape.

As such, this perspective paper delves into the realm of extemporaneous compounding, exploring its prevalence, associated risks, and the imperatives of quality assurance in ensuring safe and effective patient care. By shedding light on the diverse facets of this practice, it aims to unravel extemporaneous compounding's current standing in pharmaceutical practice and its vital role in meeting the evolving healthcare needs of the modern era.

### *Historical Evolution of Extemporaneous Compounding*

Since time immemorial, pharmacists have played a pivotal role in preparing and dispensing medicines tailored to patients' unique conditions and preferences reflecting on the dynamic interplay between medical advancements, societal needs, and the ever-changing landscape of pharmaceutical science. In ancient civilizations, healers and apothecaries were responsible for creating herbal remedies and concoctions to alleviate various ailments (Wust, 2017). These early practitioners combined botanical ingredients using traditional knowledge, often passed down through generations (Fokunang et al., 2011). With rudimentary tools and limited scientific understanding (Wust, 2017), these early forms of compounding laid the foundation for what would eventually become a critical aspect of modern healthcare.

The Middle-Age marked a period of considerable growth in the field of pharmacology. As medical knowledge expanded and scholarly works were translated, pharmacists began to explore more sophisticated techniques for preparing medications (Krantz & Hartley, 2023). Monasteries and early apothecaries became centers of herbal knowledge, and recipes for various preparations were

meticulously documented (Urlick & Meggs, 2019). During this time, compounding was heavily influenced by alchemical practices, with attempts to extract and concentrate medicinal properties from herbs and minerals (Petrovska, 2012). The Renaissance era witnessed a shift towards a more scientific approach to pharmacy. With the advent of printing, knowledge dissemination became more widespread, allowing pharmacists to access and share compounding techniques from across the world (Urlick & Meggs, 2019). This era also saw the rise of official pharmacopoeias, comprehensive texts detailing standardized formulations and compounding methods (Marriott et al., 2010). Pharmacists began to experiment with distillation, extraction, and purification techniques, laying the groundwork for the extraction and synthesis of active pharmaceutical ingredients.

The industrial revolution and subsequent advancements in chemistry marked a significant turning point in extemporaneous compounding. The isolation of pure compounds and the development of standardized dosages enabled pharmacists to move beyond traditional herbal remedies. With the emergence of pharmaceutical manufacturing, the compounding landscape shifted from the local apothecary to large-scale production facilities (Watson et al., 2020). Commercially available medicines became more accessible, reducing the need for extemporaneous compounding on a large scale. However, even as pharmaceutical manufacturing expanded, there remained a need for extemporaneous compounding to address individual patient requirements that were not met by mass-produced medications (Dooms & Carvalho, 2018). Certain patients, such as those with allergies, sensitivities, or rare diseases, required personalized formulations. Extemporaneous compounding persisted as a niche practice, albeit in a different context than its historical origins.

Today, the landscape of extemporaneous compounding is characterized by a balance between tradition and innovation. Advanced pharmaceutical knowledge, stringent regulatory standards, and sophisticated equipment have transformed the practice into a precise science (Siamidi et al., 2017). Pharmacists are equipped to create highly specialized medications, often involving complex dosage forms and precise dosing. The resurgence of interest in personalized medicine, coupled with the advent of precision therapies and orphan drugs, has rejuvenated the role of extemporaneous compounding in modern healthcare.

### **Regulatory Framework and Guidelines**

Regulatory framework and guidelines governing extemporaneous compounding have undergone a profound transformation over centuries, reflecting the growing understanding of pharmaceutical science, patient safety concerns, and the need for standardized practices in healthcare (Watson et al., 2020). The historical evolution of these regulations and guidelines reveals the intricate balance between ensuring the quality, safety, and efficacy of compounded medications while maintaining the flexibility necessary to address individual patient needs. Early history witnessed a lack of formal regulations for compounding practices. Healers, apothecaries, and early pharmacists drew upon traditional knowledge and practices to prepare medications tailored to patients' specific conditions (Wust, 2017). As medical knowledge expanded, concerns emerged regarding the inconsistent quality and efficacy of compounded products (Mohiuddin, 2019). This led to the establishment of guilds and professional associations that aimed to regulate the practice of pharmacy and ensure the competence of practitioners (Rosado et al., 2015; Britannica, T. Editors of Encyclopaedia, 1998).

The Industrial Revolution and the subsequent development of pharmaceutical manufacturing marked a significant shift in the regulatory landscape. As large-scale production of standardized medications became commonplace, the role of extemporaneous compounding was diminished. Regulatory bodies started to focus on ensuring the safety and quality of mass-produced medicines, often overlooking the unique requirements of individualized compounding (Watson et al., 2020). The mid-20<sup>th</sup> century witnessed a resurgence of interest in compounding as the limitations of mass-produced medications became apparent (Urlick & Meggs, 2019). A lack of commercially available dosage forms suitable for specific patient needs, such as pediatric and geriatric populations, led to renewed interest in extemporaneous compounding. Recognizing the need to address this gap, regulatory agencies and professional organizations began to develop guidelines specifically focused on compounding practices (Nahata & Allen, 2008).

The advent of sophisticated pharmaceutical science and technology further shaped the evolution of regulatory frameworks. The 1962 Kefauver-Harris Amendments in the United States (Greene & Podolsky, 2012), for example, highlighted the importance of demonstrating the safety and efficacy of pharmaceutical products. This emphasis on evidence-based medicine influenced the compounding landscape, prompting the establishment of more rigorous regulations. In the late 20<sup>th</sup> century and early 21<sup>st</sup> century, incidents involving contaminated or substandard compounded products raised significant concerns about patient safety. Tragic events like the 2012 fungal meningitis outbreak in the United States underscored the need for enhanced oversight of compounding practices (Teshome et al., 2014). This led to the development of comprehensive regulations, such as the Drug Quality and Security Act in the United States (Gabay, 2014), which aimed to strike a balance between maintaining access to personalized medications and ensuring patient safety.

Globalization and the increasing interconnectedness of pharmaceutical markets have also driven the harmonization of regulatory guidelines. International organizations, such as the World Health Organization (WHO) and the International Pharmaceutical Federation (FIP), have developed standards and recommendations to guide compounding practices across borders (Riley, 2004). These efforts have helped align regulatory practices and foster a more consistent approach to extemporaneous compounding worldwide.

### **Risks and Challenges**

The inherent complexity of compounding, coupled with the absence of standardized regulations and oversight, has led to concerns about patient safety, product quality, and potential adverse outcomes (Gudeman et al., 2013). Historically, the lack of clear guidelines and quality control measures for compounding has resulted in variations in the quality, potency, and stability of compounded medications. This variability introduces risks, as compounded products may not consistently deliver the intended therapeutic effect (Siamidi et al., 2017). Compounded medications are typically not evaluated or approved by regulatory authorities, and their use can lead to unintended health consequences, ranging from ineffective treatment to harmful side effects.

One of the primary challenges in extemporaneous compounding lies in achieving accurate and consistent dosing. The process involves precise calculations, measurements, and mixing of ingredients to achieve the desired dosage form. Calculation errors, misinterpretation of prescriptions, or inadequate training of compounding personnel can result in under- or over-dosing, putting patients at risk (Watson et al., 2020). Pediatric patients, in particular, are vulnerable to dosing errors due to the need for precise adjustments in medication strength (Belayneh & Tessema, 2021). Microbial contamination poses another significant risk associated with extemporaneous compounding (Gudeman et al., 2013). The compounding environment, equipment, and ingredients must be properly sterilized to prevent the introduction of harmful microorganisms. Failure to adhere to proper aseptic techniques can lead to contaminated compounded medications, which can cause serious infections or other adverse effects when administered to patients, especially those with compromised immune systems (Yuliani et al., 2023). Stability and shelf-life are crucial aspects of any medication. Compounded products may lack the rigorous stability testing and quality control measures that are common for commercially manufactured medications. This can result in the degradation of active ingredients over time, reducing the effectiveness of the medication and potentially rendering it unsafe for consumption (Belayneh & Tessema, 2021). Without proper guidance and regulations, there is a risk that patients may receive expired or unstable medications.

## AUTHOR'S PERSPECTIVE

Extemporaneous compounding occupies a unique and pivotal space in contemporary healthcare, offering both promising benefits and inherent challenges. While extemporaneous compounding presents opportunities for tailored therapeutic solutions (Nahata & Allen, 2008), it demands vigilant oversight and rigorous quality assurance measures to mitigate risks effectively. Over the course of history, extemporaneous compounding has demonstrated its adaptability and relevance in an evolving healthcare landscape. This practice has witnessed transformation through technological advancements, regulatory shifts, and changing patient needs. It is my conviction that extemporaneous compounding aligns with the ethos of patient-centered care and personalized medicine, offering an avenue to address individual variations and unique medical requirements that standardized pharmaceuticals might struggle to meet.

Nonetheless, this perspective acknowledges the potential pitfalls inherent in extemporaneous compounding (Gudeman et al., 2013). As the practice adapts to the challenges of a modern healthcare environment, concerns about formulation consistency, contamination risk, and inadequate documentation have come to the forefront. Drawing on evidence from regulatory guidelines and case studies, these risks, though not insurmountable, necessitate a thorough and standardized approach to quality assurance. The absence of such measures could undermine the very goals that extemporaneous compounding seeks to achieve - optimal patient outcomes and safety. Extemporaneous compounding's potential to enhance patient care cannot be fully realized without a rigorous commitment to quality assurance. This commitment entails collaboration between compounding pharmacists, regulatory bodies, and healthcare institutions to establish robust standards, enforce adherence, and cultivate a culture of continuous improvement.

### Novel Insights

In recent years, digital integration has reshaped various industries, and healthcare is no exception. Leveraging these technological advancements, extemporaneous compounding could experience a resurgence of innovation, leading to safer and more efficient practices (International Pharmaceutical Federation, 2020). The integration of precision measurement devices, automated compounding systems, and data-driven formulation algorithms presents a new frontier that can enhance the quality assurance process.

One of the novel insights lies in the concept of *Automation Compounding* (Meren & Waterson, 2021). This concept, rooted in real-time data analytics, assists pharmacists in calculating precise measurements, ensuring formulation consistency, and minimizing the risk of errors. By integrating the companion with electronic health records (EHRs), drug interaction databases, and patient-specific medical histories, pharmacists can make informed decisions, enhancing patient safety and overall treatment efficacy. A bold perspective on the future of extemporaneous compounding involves the creation of a *Global Compounding Consortium*. This consortium, facilitated by digital platforms, connects compounding pharmacists, regulatory bodies, and research institutions worldwide (Watson et al., 2020). By pooling expertise, sharing research findings, and collaboratively developing compounding protocols, the consortium could contribute to the establishment of universal quality assurance standards that transcend regional disparities.

By harnessing precision measurement technologies, data analytics, virtual reality training, and collaborative digital platforms, this vision embraces the challenges head-on, reimagining extemporaneous compounding as a safer, more efficient, and globally interconnected practice. This not only advances the discourse but also empowers stakeholders to explore uncharted territories, realizing the full potential of extemporaneous compounding in the 21<sup>st</sup> century healthcare landscape.

## DISCUSSION

### *Prevalence of Extemporaneous Compounding*

Compounding of extemporaneous preparations is still a popular global practice in health institutions and pharmacies in spite of advanced pharmaceutical manufacturing industry since commercially available dosage forms fail to meet the requirements of all patients (Yuliani et al., 2023). A significant number of pharmacies provide compounding services but the prevalence of extemporaneous dispensing is generally low, estimated to be less than 5% of health products (Wiedyaningsih et al., 2017). Generally, prevalence is higher for dermatological and pediatric products due to unavailability of commercial preparations that are tailored towards a specific patient condition (Moulis et al., 2018; Fátima, 2017; Pappas et al., 2002). A comprehensive literature searches for the period (1996-2015) revealed that the occurrence of extemporaneously compounded products in most pharmacies in United Kingdom, New Zealand, Belgium, France, Australia and the Netherlands to be less than 5% (Kristina et al., 2017). In the United States (US), compounding is carried out in both the inpatient and outpatient pharmacies, with a tendency towards larger scale outpatient production (Watson et al., 2020). Nearly 7,500 community-based pharmacies in the US are engaged in extemporaneous compounding. Extemporaneous preparation usage in Indonesia accounted for less than 5% of all prescriptions (Kristina et al., 2017). Approximately 2 % of 126,840 prescriptions dispensed in Palestine in 30 days were extemporaneously prepared. (Zaid et al., 2012).

The practice of extemporaneous compounding continues to increase despite the low percentage of these products in relation to licensed products. About 70% of the community pharmacies in Latvia provided compounding services but the sales of extemporaneous medicine were found to be 0.65% of commercial products. This was similar to the results obtained for Finland and Spain (Kiseļova et al., 2019). Prevalence of extemporaneous preparations in Jordan was 51.7% and dermatological products were the most commonly compounded products (AlKhatib et al., 2019). In Ethiopia, about 5% of 353 operating hospitals in the nation had dermatologic compounding facilities in the year 2020 (Selam & Ababu, 2021). In a study conducted at a teaching hospital in Nigeria, all the extemporaneous preparations were liquid dosage form prepared from crushed tablets, capsules and parenteral dosage forms (Yusuff, 2019). A study performed at Kenyatta hospital, Kenya to evaluate extemporaneously prepared products derived from oral solid dosage form alterations, a total of 392 oral liquid formulations were compounded over the study period of January, 2012 to December, 2013. Oral suspensions were the most frequently compounded products. The study showed that there is a greater need for oral liquid dosage forms in comparison with other dosage forms (Bilakhia et al., 2018). These results concur with a study in Brazil which revealed that there was no commercially available liquid form for a significant number of solid dosage forms as represented in Table 1 (Silva et al., 2020).

**Table 1:**

#### *Liquid Preparations Formulated from Solid Dosage Forms*

Acetazolamide	Clobazam	Hydrochlorothiazide	Metoprolol	Quinapril
Alprazolam	Clomipramine	Idebenone	Minocycline	Ribavirin
Amlodipine	Clonazepam	Imatinib	Minoxidil	Saquinavir
Aripiprazole	Clonidine	Imipramine	Moxifloxacin	Sildenafil
Atorvastatin	Dapsone	Isotretinoin	Nadolol	Sotalol
Bosentan	Diazoxide	Lapatinib	Naltrexone	Sulfadiazine
Capecitabine	Diltiazem	Levodopa	Naproxen	Sulfasalazine
Captopril	Enalapril	Levofloxacin	Norfloxacin	Tacrolimus
Carbidopa	Erlotinib	Lisinopril	Oseltamivir	Terbinafine
Carvedilol	Flecainide	Loperamide	Pentoxifylline	Tiagabine

Celecoxib	Folicacid	Lorazepam	Phenobarbital	Topiramate
Chloroquine	Furosemide	Melatonin	Phenytoin	Trimethoprim
Chlorpromazine	Gabapentin	Metformin	Propafenone	Vancomycin
Cinacalcet	Glibenclamide	Methadone	Propranolol	Valsartan
Cholecalciferol	Haloperidol	Methotrexate	Pyridoxine	Warfarin

(Silva et al., 2020)

A majority of these products require stringent control of the dose level to achieve the intended effect. The list includes products such as warfarin which have a narrow therapeutic index, whereby there is very small margin between a safe and lethal dose and hence, require very careful dosing. Splitting of these tablets may result in variation of dose uniformity and therapeutic levels of the drug substance.

### **Risks Associated with Extemporaneous Compounding**

Extemporaneous preparations are designed for an individual patient and are neither evaluated nor licensed by Drug Regulatory Authorities (DRAs). In addition, they are not subjected to strict quality control and stability testing during preparation. Furthermore, these preparations lack product prescribing information standard. Consequently, there is considerable risk associated with the use of compounded products and more so when given to vulnerable patients; children and the elderly. The probable risks include calculation errors, microbial contamination and toxicity of some ingredients. Adverse effects and stability noncompliance may occur in pediatric patients due to drug/excipient incompatibilities and drug degradation (Yuliani et al., 2023; Rouaz et al., 2021; Yuliani et al., 2020; Lee et al., 2018). Excipients of concern in children include sorbitol, lactose, aspartame, mannitol, tartrazine and azo dyes (Yuliani et al., 2023). Limited expertise in formulation of these products and inadequate compliance to manufacturing practices aggravate the risk of these products. Preparation of a pediatric suspension from a solid dosage form may provide variable dosing because suspensions require suspending agents for even distribution of the drug substance. Weight of split tablets varied from of 50-150% of the actual half-tablet (Patel et al., 2011).

Numerous publications have reported *grievous* noncompliance in compounding of extemporaneous preparations. In USA, a 5-year-old child died from an overdose of clonidine arising from a calculation error (Kirsch, 2005). In Massachusetts, USA, 100 patients died after receiving contaminated parenteral injections of methylprednisolone acetate (Editors at U.S. Attorney's Office, 2021; Alkhatib et al., 2019; Pew Charitable Trusts, 2017). A study on pharmaceutical compounding in the USA during the period 1990 to 2020 identified 27 contamination errors which affected 1119 patients. Microbial contamination is common in bulk production of compounded parenteral products and affect more patients. Another research report indicated that compounded preparation containing gentamicin and hydrocortisone for dermatological application was contaminated with objectionable microbes; *Pseudomonas aeruginosa*, *Salmonella* spp., *Staphylococcus aureus*, and *Escherichia coli* (Hapsari et al., 2019).

In view of the health hazards related to compounding of pharmaceutical products, comprehensive risk assessment and mitigation are obligatory to ensure product quality. Important considerations include design of compounding area, personnel competencies, equipment, ingredients and packaging materials. It is prudent to consider possible alternatives that will give the greater assurance of therapeutic effectiveness and safety before deciding to compound the product. Alternatives include therapeutic substitution, procurement options, manufacturing the product in a licensed facility, use of dosage form intended for another route. Risk is also reduced by use of standard and validated formulae where possible. Rigorous risk assessment ascertains the need for extemporaneous compounding. It also aids in categorization of the product on the basis of the probability of related risks during the preparation of the product. Table 2 and Figure 1 present the product classification and risk assessment matrix, respectively. The products are classified as low, medium, or high risk and this commensurate the level of stringency during the preparation process. High risk compounding requires specialized facilities and equipment, validated processes, stringent control of cross contamination, safe handling and disposal procedure. The pharmacist under whose authority these products are compounded is

responsible for assuring their quality. Pharmacists engaged in complex compounding should therefore demonstrate knowledge and competency that are required for the operations.

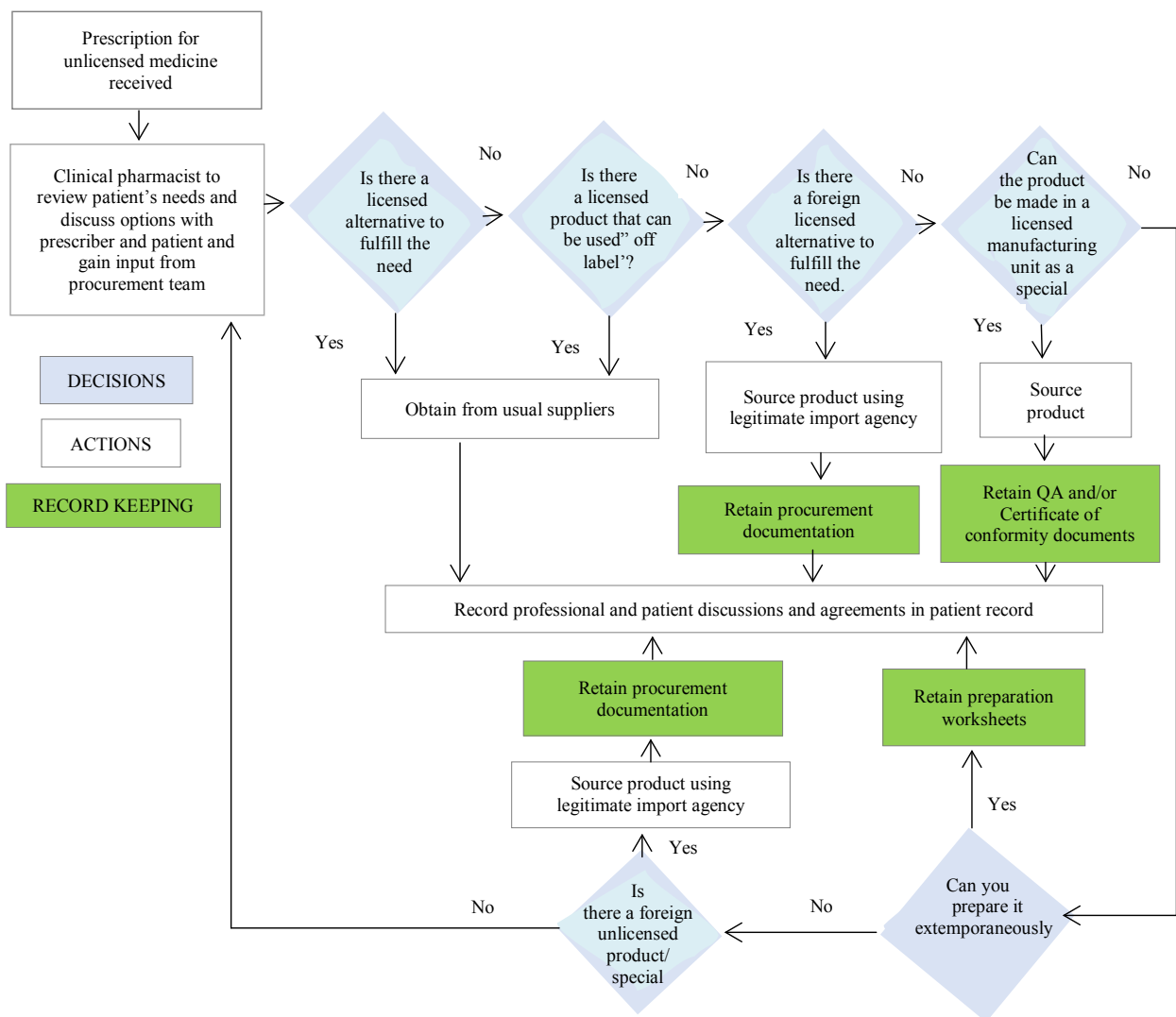
**Table 2:**  
**Risk Matrix for Product Categorization**

Low	Medium	High
Validated formula	Unvalidated formula	No Formula
Existing stability data	No stability data	Sterile products, cytotoxic,
Minimal toxicity	Minimum toxicity	Hormones, Narrow therapeutic
Short shelf life	Wide therapeutic window	window
Non sterile products	Non sterile products	Special handling

Source: Handbook of Extemporaneous Preparation

**The NHS Pharmaceutical Quality Assurance Committee 2010**

**Figure 1:**  
**Risk Evaluation-Extemporaneous Medicines Decision Tree**





## Quality Assurance of Extemporaneous Preparations

Pharmaceutical Quality Assurance (QA) covers all aspects pharmaceutical manufacturing that impact quality of products. A drug product is construed as fit for use if it meets its established quality attributes and has been manufactured in accordance with Good Manufacturing Practice (GMP) regulations. Pharmaceutical manufacturers are required to adhere to Quality by Design principals as prescribed in the guidelines; ICH Q8 (R2) (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System). A good quality product represents low risk of contamination and failure to achieve the desired clinical attributes (Goyala & Gupta, 2021). Quality requirements of drug products are provided in the GMP guidelines and pharmacopeial monographs which stipulate the standard for specifications and the analytical techniques. In the case of non-pharmacopeial products, methods of analysis are developed by the manufacturer, validated and submitted to the regulatory authority for evaluation as part of market authorization dossier (Yu et al., 2014). Extemporaneous preparations are not subjected to product development, and are not reviewed to evaluate their safety, clinical efficacy and stability before they are dispensed to the patient.

Extemporaneous preparations are associated with quality concerns related to the drug product and the compounding process. Challenges in extemporaneous compounding practices have been reported in some countries, including limited competence among staff, unqualified facilities, lack of quality control, absence of national formula guidelines for extemporaneous preparations in many countries, assurance of stability and insufficient information on the age-appropriateness of dosage forms (Seid et al., 2017; Alfred-Ugbenbo et al., 2016). Also, there are no international harmonized standards or legislation with regard to compounding and control of these medicinal products (Hamishehkar et al., 2015).

A cross-sectional study in Ethiopia with 300 participants including physicians and pharmacists indicated inconsistency of compounded medication quality. Respondents strongly believed that poor quality extemporaneous antimicrobials contribute to anti-microbial resistance development (Assefa et al., 2022). Many pharmacies and institutions develop their own formulary for the frequently compounded products, but this is not sufficient to reduce the possibility of error (Smith et al., 2019). Development of national standard formulary for these preparations is essential in reduction of the risks (Pharmaceutical Society of Australia, 2015; Editorial board of Pharmaceutical Services Division, MOH, 2012; Jackson & Lowey, 2010). Drug Regulatory Authorities recognize the risks associated with extemporaneous compounding and have developed guidelines to ensure product quality, safety and efficacy. These products should comply with all the GMPs including the design of compounding areas. All ingredients of the compounded product, that is, the drug substance and the excipients, are subject to pharmacopeial quality standard and should be sourced from approved vendors (Falconer & Steadman, 2017).

The level of regulation corresponds to the risk represented by the products. Simple extemporaneous dispensing is considered as low risk compared to preparation of quantities of product to meet anticipated needs of patients in a hospital setting which requires accreditation of the premises, practices and certification of the pharmacist. Pharmacists performing simple compounding process should have the appropriate education and training deemed competent to undertake the task. Complex compounded products such as sterile preparations, products containing ingredients that pose occupational health and safety hazard such as hormones require specific competencies such as handling of complex processes, operating equipment and maintaining the required clean room standard to arrest the high risks related with the processing of these medicines (Pharmacy Board of Australia, 2015).

In the UK, Medicines Guidance for Specials Manufacturers of 2021 provides comprehensive GMP requirements to be applied when manufacturing unlicensed medicines. The system should be documented, monitored and includes the aspects presented in Table 3. The competencies that are required in compounding are presented in Table 4. The WHO technical guidelines of 2016 provide points to be considered for pediatric preparations that are not available as licensed product. The guidelines also provide information on alternatives to compounding of medicines for pediatric patients (WHO, 2016). The USP Convention specifies standards, the process, testing, and verification of compounded products. Chapters 797 and 795 of the pharmacopoeia, apply to the compounding of sterile and nonsterile preparations respectively. In addition, it provides comprehensive information on Pharmaceutical Calculations in Pharmacy Practice, Quality Assurance in Pharmaceutical Compounding,

### Prescription Balances and Volumetric Apparatus used in Compounding.

Regulatory guidance requires product expiry dates for extemporaneous all preparations which should be based on a scientific rationale, including test data. In the absence of stability information, the USP presents maximum Beyond Use Dates (BUD) for Non-preserved aqueous, Preserved aqueous, Nonaqueous dosage forms and solid dosage forms as 14, 35, 90 and 180 days respectively. Oral pediatric extemporaneous preparations are common especially in developing countries such as Kenya, Nigeria and Ethiopia. Stability studies have been performed on some of the pediatric formulations (Lin et al., 2021; Silva et al., 2020; Thrimawithana et al., 2018; Glass & Haywood, 2006). Results of a review on stability of 28 oral pediatric extemporaneous preparations in Ethiopia showed that most formulations were chemically, physically, and microbiologically stable and retained more than 90% of the initial content (Belayneh & Tessema, 2021). In Saudi Hospital Pharmacies, oral powders and capsules filled with the powder of crushed tables were stable for up to 6 months (Prasanthi, 2014). Similarly, a study in Damanhur, Egypt, showed that bisoprolol suspension remained stable throughout the 6-month period regardless of the storage conditions (El-Masry et al., 2022).

**Table 3:**

#### **MHRA Guidance for Specials Manufacturers Rev. 2 – Jan 2021**

Quality Assurance components	
<ul style="list-style-type: none"> <li>• Proper design and maintenance of compounding area</li> </ul>	<ul style="list-style-type: none"> <li>• Authorized personnel are allowed in the compounding operations</li> </ul>
<ul style="list-style-type: none"> <li>• Good compounding practices as per the guidelines.</li> </ul>	<ul style="list-style-type: none"> <li>• Compounding procedures are adequate for preventing errors.</li> </ul>
<ul style="list-style-type: none"> <li>• Personnel training &amp; qualification to perform duties</li> </ul>	<ul style="list-style-type: none"> <li>• Documentation and verification of compounding activities</li> </ul>
<ul style="list-style-type: none"> <li>• Quality of raw materials and appropriate Equipment</li> </ul>	<ul style="list-style-type: none"> <li>• The compounding environment is suitable for its intended purpose</li> </ul>
<ul style="list-style-type: none"> <li>• Formularies and compendia availability</li> </ul>	<ul style="list-style-type: none"> <li>• Release of product by the pharmacist</li> </ul>
<ul style="list-style-type: none"> <li>• Evaluation of drug product</li> </ul>	<ul style="list-style-type: none"> <li>• Stability of product</li> </ul>

**Table 4:**

#### **Preparation of Extemporaneous Medicines; Performance Criteria (SFHPHARM11)**

Compounder Competence	
<ul style="list-style-type: none"> <li>• To check prescription and select the correct formula.</li> </ul>	<ul style="list-style-type: none"> <li>• Prepare the product according to procedure.</li> </ul>
<ul style="list-style-type: none"> <li>• To confirm the compounding area is clean and ready for use.</li> </ul>	<ul style="list-style-type: none"> <li>• Critical process evaluation.</li> <li>• Pack and label the product correctly</li> </ul>
<ul style="list-style-type: none"> <li>• To select the correct equipment for the process and the product.</li> </ul>	<ul style="list-style-type: none"> <li>• To complete all relevant documentation</li> </ul>
<ul style="list-style-type: none"> <li>• To confirm that the correct worksheet, labels, ingredients, are available and approved before start of the preparation.</li> </ul>	<ul style="list-style-type: none"> <li>• To clean the work area and equipment following the activity</li> <li>• To analyses the product and evaluate the results</li> </ul>
<ul style="list-style-type: none"> <li>• To calculate and measure the ingredients according to formula requirement</li> </ul>	<ul style="list-style-type: none"> <li>• Product release procedure</li> </ul>

Stability is a basic determinant of product quality, efficacy and safety. Most extemporaneous preparations are considered stable if they retain more than 90% of the content of the drug substance that is stated on the label. Each preparation is distinct and requires stability testing tailored to the specific quality parameters. Apart from few preparations, mostly pediatric formulations, literature on stability of extemporaneous products under storage conditions and distribution packs for most of these formulations is limited. Drug products are prone to physical, chemical and microbiological instability. Drug molecules with multiple functional groups are more easily degraded. The degradation pathways include hydrolysis, oxidation, decarboxylation, photodegradation, dehydration as shown by examples in Table 5 (Bhangare et al., 2022; Gabrič et al., 2022; Hotha et al., 2016). Extemporaneous preparations require stability evidence as an assurance of product quality.

**Table 5:**  
**Degradation of Compounded Preparations**

Degradation factors	Affected group	Examples
Drug substance concentration	Acetals, amides	Aspirin, atenolol, atorvastatin, baclofen, captopril, digoxin, diazepam, diphenoxylate, heparin, hydrocortisone, lignocaine
Solvent	Aldehydes, alcohols, anhydrides, carboxylic acids	methylphenidate, norfloxacin, omeprazole
Temperature	esters, ethers,	Paracetamol, penicillins, progesterone, quinine, sildenafil, simvastatin, testosterone
Light	lactams, lactones	
Excipients	sulfonamides	

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Extemporaneous compounding is experiencing a resurgence especially in pediatric preparations. In South Africa, an association of Compounding Pharmacists was formed in 2013 to promote the practice of compounding and also accelerate communications with the regulatory authorities and the public on matters concerning extemporaneous products. The aim is to establish a consistent system of quality standard for these products. A standard quality can be achieved by adhering to harmonized good manufacturing standard and national formularies for these products.

## CONCLUSION

In summary, the exploration of extemporaneous compounding has unveiled a complex tapestry woven with historical roots, contemporary challenges, and evolving solutions. As we navigate this intricate landscape, we reiterate the central viewpoint that underscores the vital role of extemporaneous compounding in personalized medicine and patient-centered care. The resurgence of extemporaneous compounding comes as a response to the growing need for tailored medications that align precisely with individual patient requirements. It serves as a bridge between the limitations of commercially available dosage forms and the imperative to provide therapeutic solutions that cater to a diverse range of patient needs. The practice of extemporaneous compounding is an intricate amalgamation of skill, precision, and scientific knowledge—an art that requires both technical mastery and a deep sense of responsibility towards patient safety. Amid the resurgence, a landscape of risks and challenges emerges. From calculation errors to microbial contamination, the risks associated with extemporaneous compounding underscore the need for robust quality assurance measures. The absence of standardized practices, the lack of harmonized regulations, and the dearth of comprehensive stability testing strategies necessitate concerted efforts to establish a foundation of safety and efficacy for compounded products. While the challenges persist, we envision a future where extemporaneous compounding thrives within a framework of international harmonization and stringent quality control. The practice can be

fortified through the development of national formularies, adherence to standardized manufacturing procedures, and the fostering of pharmacist competencies in complex compounding processes. The growing awareness of the risks associated with compounded products is prompting regulatory bodies to institute guidelines and standards, paving the way for a safer landscape. This paper echoes the call for increased dialogue, research, and education in the realm of extemporaneous compounding. It is crucial that learning institutions emphasize the significance of pharmaceutical compounding, equipping graduates with the skills and knowledge required to navigate this specialized field. Collaborative efforts between pharmacists, healthcare institutions, and regulatory bodies are essential to cultivate a culture of quality and safety in extemporaneous compounding.

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