Pharmacy compounding plays a vital role in patient treatment and care. When drug shortages occur, or when patients have unique needs that standard medications cannot meet, pharmacy compounding often fills the gap. However, the practice of pharmacy compounding has received increased scrutiny in recent years because of concerns about safety, quality, and oversight.

This article looks at these issues and provides an overview of pharmacy compounding, reviews the regulations that govern compounding, explores the risks associated with compounded medications, and provides guidance for proactively managing those risks.

A Historical Perspective

Pharmacy compounding, in its traditional form, is an essential service that helps many people who have special needs. “Traditional” compounding refers to pharmacists preparing prescriptions on an individual basis, for a specific patient and based on a single order from a licensed provider.

The practice of pharmacy compounding has existed for many years and has seen dips and peaks in demand. In recent years, as the need for customized or short-supply medications has increased, so has the demand for compounding. Estimates suggest that the compounding industry currently makes up about 1-3 percent of the U.S. prescription market ($300 billion overall).1
Doctors and patients may turn to compounding pharmacies for numerous reasons. For example, these pharmacies can provide medications for patients who have unique needs, such as those who require special dosages or who have allergies to components of manufactured drugs, such as dyes or gluten. Compounders also can prepare alternative forms of medications by, for example, creating patches or syrups in place of pills.

One of the most critical areas in which compounding plays a role is with drug shortages. Compounders might be called upon to produce vital medications and products that are in short supply as a result of problems with large drug manufacturers. Additionally, some manufacturers may stop producing medications when they are no longer economically viable or when they only serve a limited population. When this occurs, compounding pharmacies may step in to provide these medications to patients who still require them.

**Oversight and Regulation**

**State Pharmacy Boards**

Unlike drug manufacturers, which are regulated at the federal level, compounding pharmacies generally are licensed and regulated by state pharmacy boards. Depending on the nature and function of the pharmacy, some also are registered with the U.S. Food and Drug Administration (FDA) or the Drug Enforcement Administration (DEA). Historically, however, authority over compounding pharmacies has largely resided with the states.

Regulations and standards vary from state to state, but most state laws incorporate some or all aspects of the United States Pharmacopeia-National Formulary (USP-NF) standards for sterile compounding (USP <797> Pharmacy Compounding—Sterile Preparations) into their regulations governing compounding pharmacies.

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**Did You Know?**

- Slightly more than three-fourths of independent pharmacists compound medications for patients.
- Almost 100 percent of hospitals compound medications.
- Almost all home health specialty pharmacies compound medications.²
USP <797> is a comprehensive set of standards that provides guidance on the appropriate procedures and requirements for compounding sterile preparations. These standards describe in detail the acceptable conditions and practices that will help prevent issues with contamination, variability in strength, poor quality ingredients, and other factors that may compromise quality.

In a 2018 assessment of state oversight of compounding pharmacies, The Pew Charitable Trusts (Pew) and National Association of Boards of Pharmacy (NABP) found that 32 state pharmacy boards require full compliance with USP <797>, while 11 states have requirements that are considered equivalent to or stricter than USP <797>. A few states require compliance with other quality standards, while only one state – Kansas – currently does not enforce any quality standards (although policy changes are pending).

**U.S. Food and Drug Administration**

The FDA has authority and responsibility for the oversight of commercial drug manufacturing in the United States. However, the FDA’s authority to oversee and regulate compounding pharmacies has been a much debated and ambiguous area for years. With the bulk of oversight residing with individual states, the FDA generally has been limited in its ability to regulate and direct enforcement against compounding pharmacies.

Efforts to broaden FDA oversight over the years have been delayed or failed. A 1997 federal policy on compounding was invalidated by the courts but later revived in modified format as part of the Federal Food, Drug, and Cosmetic Act (FDCA). Additionally, attempts were made in 2003 and 2007 to establish an FDA oversight committee on pharmacy compounding and to put in place restrictions and requirements for sterile compounding, respectively. However, both of these efforts were unsuccessful.

Then, in 2012, pharmacy compounding received widespread and critical attention in the wake of a national fungal meningitis outbreak linked to compounded epidural steroid injections. The resulting deaths of more than 70 patients and sickening of hundreds more led to renewed...
calls for better regulation of compounding pharmacies. The FDA announced the need for clarification on the regulatory roles surrounding compounding, including better oversight to determine when compounding pharmacies move beyond their traditional roles into drug manufacturing.

In October 2012, the Institute for Safe Medication Practices (ISMP) called on Congress to address regulatory gaps and increase the FDA’s authority to oversee compounding pharmacies that distribute medicines in mass quantities, manufacture sterile products from nonsterile active ingredients, and/or distribute products across state lines.5

These concerns and requests culminated in the Drug Quality and Security Act (DQSA), which was signed into law in November 2013.6 Title 1 of the law, the Compounding Quality Act (CQA), makes a distinction between pharmacies engaged in traditional compounding and those considered “outsourcing facilities” — that is, companies that are compounding products without patient-specific prescriptions for healthcare organizations to keep on hand as office stock.

Traditional compounding pharmacies are regulated under Section 503A of the FDCA, and state boards of pharmacy continue to have primary oversight over these pharmacies. Outsourcing facilities, on the other hand, are regulated under Section 503B of the FDCA, which requires stricter FDA oversight and adherence to current good manufacturing processes (CGMPs). However, by registering as outsourcing facilities, these companies “are permitted to sell unlimited quantities of compounded drugs without a prescription anywhere in the U.S. and are exempt from the drug approvals process.”7

The 2018 assessment from Pew and NABP explains that the dual regulatory framework for compounding pharmacies depends on states enforcing the prescription requirement and prohibiting traditional pharmacies from compounding sterile office stock. In the absence of enforcement, “outsourcing facilities have
no incentive to register with FDA and adhere to the more rigorous quality standards that are appropriate for bulk production and longer shelf life."

For more information about the FDA’s role in overseeing compounding pharmacies, see Compounding and the FDA: Questions and Answers.

**Accreditation**

In 2007, a number of leading pharmacy organizations founded the Pharmacy Compounding Accreditation Board (PCAB) as part of an effort to establish a consistent system of quality standards for pharmacy compounding and address concerns about the safety of compounded medications. In 2014, PCAB accreditation became a service of the Accreditation Commission for Health Care (ACHC).

Although accreditation through ACHC/PCAB is voluntary, earning the designation shows that a pharmacy “demonstrates a commitment to meeting the highest industry standards for quality and safety.”

Pharmacies seeking voluntary accreditation through PCAB undergo a six-step process, including an onsite evaluation. The evaluation assesses a number of factors, including staff training and competency, patient records, compounding processes, performance improvement and quality assurance initiatives, recordkeeping, and policies and procedures.

Once the PCAB designation has been earned, pharmacies undergo routine onsite evaluations every 3 years to maintain their accreditation.

**Patient Safety and Risk Management Concerns**

Although pharmacy compounding has filled a vital gap for providers, patients, and healthcare organizations with unique or immediate needs, it has not been without risks. As the 2012 fungal meningitis outbreak proved, the effects of compounding errors can be widespread and devastating. Although the fungal meningitis outbreak was unprecedented in scale, adverse events related to pharmacy compounding are not an anomaly.
In the past 20 years, numerous reports of medication errors linked to compounding have emerged, and these errors have led to a series of infections, overdoses, and fatalities. For example, in 2005, 10 patients in Maryland died after receiving contaminated cardioplegia solution; in 2011, nine patients in Alabama died from contaminated parenteral nutrition solutions; and in 2016, a child died after taking a compounded oral liquid that contained the wrong medication.\textsuperscript{12}

An investigation by Pew’s Drug Safety Project found that compounding errors were linked to more than 1,200 adverse events, including 99 deaths, from 2001 through 2017. Further, the actual number of adverse events due to compounding errors during this timeframe was likely higher due to underreporting of these issues.\textsuperscript{13}

Although health experts generally agree that when practiced in its traditional form, compounding serves an essential public health function, a number of factors — such as inadequate oversight, poor compounding practices, and lack of adverse event reporting — can increase the risks associated with pharmacy compounding.

**Inadequate Oversight**

As discussed earlier, compounding pharmacies historically have not been subject to the strict federal regulations that govern drug manufacturing. As such, the FDA warns that compounded medications are not FDA approved and, thus, their safety and effectiveness have not been verified.\textsuperscript{14}

Although state pharmacy boards have the authority and responsibility to oversee pharmacy compounding, regulations vary among states, which has led to inconsistencies in practice and enforcement. An article in *STAT* noted that oversight of compounding pharmacies “is a spotty patchwork of regulations, raising questions about the ability to protect the public health.”\textsuperscript{15}

Yet, progress has been made in the last few years. Pew’s 2015 assessment of state oversight of compounding pharmacies showed that only about half of states required pharmacies that...
make sterile medications to fully comply with USP <797>. Further, 65 percent allowed pharmacies to compound without patient-specific prescriptions (i.e., office stock medications and products).16

In comparison, Pew’s 2018 assessment notes that the majority of states now adhere to recommendations in two key areas identified as best practices for state oversight:

1. Requiring traditional compounding pharmacies to comply with recognized quality standards

2. Prohibiting traditional compounding pharmacies from producing sterile office stock for human use

However, the 2018 assessment also points to ongoing areas of concern and opportunities for improvement in oversight. For example, 11 states have policies that conflict with the FDCA in relation to the production of office stock medications and products.

Additionally, the number of states that perform routine inspections of traditional compounding pharmacies has decreased, possibly due to lack of proper resources to provide oversight. The growth of pharmacy compounding in recent years and insufficient funding are both likely contributors to this problem. Unfortunately, lack of consistency in how states oversee compounding practices and inadequate resources can create gaps in oversight, which in turn can allow poor practices to go undetected.

**Poor Compounding Practices**

Poor practices and inadequate quality control have led to product contamination and problems with the strength, quality, and purity of some compounded medications. For some pharmacies, these problems have likely arisen as a result of a shift from traditional compounding to activities more closely resembling drug manufacturing, such as mass production and interstate distribution.
For example, the pharmacy involved in the 2012 fungal meningitis outbreak shipped about 17,000 vials of potentially contaminated steroid injections to 75 clinics in 23 states, and reports suggested that the contaminated doses were mass-produced over a 3-day period.\textsuperscript{17} For this reason, the increasing number of states that require compounding pharmacies to comply with FDCA regulations related to outsourcing facilities and producing office stock is promising.

However, the reduced number of states conducting inspections is concerning because lack of consistency in testing compounded drugs also contributes to poor practice and failed quality control. Although conducting annual inspections of facilities that perform sterile compounding is a best practice recommendation, “the frequency of inspections for traditional pharmacies located in a given state is not typically dictated by that state’s laws or regulations, but is instead often based on resources.”\textsuperscript{18}

The frequency of inspections varies across states and sometimes within states based on certain criteria. Pew’s 2018 assessment notes that 22 states and the District of Columbia conduct routine inspections of traditional compounding pharmacies at least once a year. Other states reported 18-month, 2-year, 3-year, and 5-year inspection intervals. A few states base inspection frequency on a risk stratification model, in which pharmacies performing high-risk sterile compounding receive more frequent inspections compared with those performing medium- and low-risk compounding.\textsuperscript{19}

The practice of shipping compounded medications across state lines also has implications for the quality and safety of these products. As with other aspects of compounding regulation, the requirements and regulations that states impose in relation to out-of-state compounding quality and inspections varies. Pew advises states to (1) require out-of-state traditional compounding pharmacies that ship into the state to adhere to USP quality standards at a minimum, and (2) subject out-of-state pharmacies to the same frequency of inspections as in-state pharmacies, whether conducted by the state or a third party.\textsuperscript{20}

Another quality concern with compounded medications stems from the source of pharmaceutical ingredients used for drug compounding. Although compounding guidelines and standards dictate that pharmacies should use pharmaceutical-grade ingredients from FDA-registered or licensed facilities, some compounding pharmacies have turned to nonregistered
factories overseas to supply their drug components. Without appropriate regulatory oversight, the safety and quality of these ingredients are unknown.

**Lack of Reporting**

Commercial drug manufacturers are required by law to notify the FDA if they learn that their medications or products have caused adverse outcomes or patient harm. However, because compounding pharmacies operate under a different regulatory structure than commercial manufacturers, historically they have had no legal requirement to report to the FDA adverse events linked to their products.

When problems associated with compounding have come to light, it has been through voluntary reporting, the media, and scientific literature. As a result, the actual scope of compounding-related errors is unknown. Additionally, limited reporting of adverse outcomes results in inadequate data, which might hinder efforts to evaluate gaps in regulation, process, and safety.

In recent years, attempts have been made to address adverse event reporting. With the implementation of the DQSA, a distinction was made between traditional compounding pharmacies and outsourcing facilities (as described on page 4), and that distinction has led to a differentiation in reporting requirements.

Under section 503B, outsourcing facilities are required to submit adverse event reports to the FDA; failure to do so can result in regulatory and enforcement action. In 2015, the FDA released a guidance document for outsourcing facilities that explains what to report, the threshold for reporting, requirements for follow-up reports, details about essential data elements, and other key information.\(^2\) Traditional compounding pharmacies continue to be regulated by states; thus, they have no legal requirement to report adverse events to the FDA.

**Risk Mitigation Strategies**

Although problems and risks associated with pharmacy compounding have received increased attention since the 2012 fungal meningitis outbreak, the healthcare community still recognizes the necessity of compounding in patient care. When drug shortages occur, or when
patients have unique needs that “one-size-fits-all” medications cannot meet, pharmacy compounding often fills the gap.

Thus, the question becomes, “What is the best way to mitigate the risks associated with pharmacy compounding?” An ISMP Medication Safety Alert advises that, whenever possible, providers should use or prescribe FDA-approved products from pharmaceutical manufacturers.22

If FDA-approved medications and products are not commercially available, providers should carefully assess compounding pharmacies before using their services. Due diligence of compounding services requires evaluating a range of criteria, including pharmacy history, licensing, safety precautions, quality assurance processes, staff education, and more. MedPro’s checklist titled Assessing Pharmacy Compounding Services provides a high-level overview of the types of issues that should be considered when performing due diligence of compounding services. More detailed information about pharmacy compounding can be found in the American Society of Health-System Pharmacists’ Sterile Compounding Competency Library.

**In Summary**

Increased scrutiny of pharmacy compounding, largely due to the 2012 fungal meningitis outbreak and resultant patient harm, has brought to light concerns about the safety, effectiveness, and oversight of pharmacy compounding. As healthcare officials, legislators, and the compounding industry continue to negotiate shifting boundaries and gray areas of regulation and enforcement, healthcare organizations and providers can take a proactive approach to safety.

Understanding the risks associated with compounding and taking steps to ensure that staff are performing due diligence when purchasing compounded medications can help safeguard your organization’s medication inventory and address concerns about patient safety.
Endnotes


2 Ibid.


6 Public Law No. 113-54 — Drug Quality and Security Act.

7 The Pew Charitable Trusts, National assessment of state oversight of sterile compounding.


13 The Pew Charitable Trusts and the National Association of Boards of Pharmacy, State oversight of drug compounding.


Pew Charitable Trusts, National assessment of state oversight of sterile compounding.


The Pew Charitable Trusts and the National Association of Boards of Pharmacy, State oversight of drug compounding.

Ibid.

Ibid.


ISMP, Sterile compounding tragedy.

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