Pharmaceutical compounding: Safeguarding the patient, worker and environment

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Introduction

Pharmaceutical compounding – formulating custom medications for patient-specific clinical needs – is as old as pharmacy itself. Despite the availability of thousands of mass-produced pharmaceuticals with standardized strengths and dosages, compounding remains an integral part of pharmaceutical practice.

The majority of pharmacies, including chain drug stores, report they do some compounding, formulating 30 to 40 million prescriptions a year.[1] In October 2012, pharmaceutical compounding made headlines when the New England Compounding Center (NECC) in Massachusetts was found responsible for a 20-state fungal meningitis outbreak caused by contaminated injectable steroids that killed 76 people and sickened 778 more.[2]

The NECC tragedy revealed gaps in compounding regulation and oversight that federal and state agencies, accrediting bodies and industry organizations are still working to close. The continuing incidence of adverse events that have caused illness sustains the urgency of these efforts and death.[3]

Six years later, improved coordination among the responsible agencies and updated standards from the United States Pharmacopeia (USP) Convention are raising the bar for compounding pharmacies of every size and in every setting. However, given that compliance with the standards in their current form is inconsistent among hospital-based compounding pharmacies, health systems have significant work and investment to do to make sure that their compounding facilities, staff and processes meet the requirements.

Defining pharmaceutical compounding

The USP defines compounding as “The preparation, mixing, assembling, altering, packaging and labeling of a drug, drug-delivery device or device in accordance with a licensed practitioner's prescription, medication order or initiative based on the practitioner/patient/pharmacist/compounder relationship in the course of professional practice.”[4]

Through compounding, pharmacists create customized medications for patients whose clinical needs can’t be met by commercially available products approved by the Food and Drug Administration (FDA).

Types of compounding

There are three types of compounding: nonsterile, sterile and hazardous drug compounding.

- **Nonsterile compounding** is the creation of medication doses for patients to drink, swallow, insert or apply to the skin. This kind of compounding can
  - Broaden options for children and seniors (e.g., by making oral liquids better tasting or by converting tablets or capsules into liquids for patients with swallowing problems)
  - Allow for alternative drug delivery methods (such as topical or transdermal administration through gels or creams)
  - Accommodate environment- and cosmetic-sensitive patients (by adjusting eliminate potential allergic reactions)
- **Sterile compounding** is the creation of medication doses that are required to be free of microorganisms (bacteria, fungus, endotoxins, pyrogens) because they’re injected or administered directly to an area highly susceptible to infection, such as the eye, bladder or lungs. These products may not be commercially manufactured due to the need for patient-specific dosage adjustments or short stability.
- **Hazardous drug compounding** is the preparation of nonsterile or sterile dosage forms of drugs that may pose an exposure risk to the handler, patient or environment.

The inherent risks of compounding

Compounding risks fall into three main categories: errors, contamination and hazardous drug (HD) exposure. The safety and efficacy of compounded medications depend on multiple complex elements:

- The skill and judgment of the pharmacist
- The quality and quantity of ingredients (many of which are hazardous)
- The efficiency of processes
- The cleanliness of facilities
- The provision of safe packaging and handling throughout the chain of custody

These factors, and more, must all come together consistently to produce medications that help instead of harm.

Errors

Medication compounding is often perceived as a simple, uneventful task, even by healthcare professionals. However, in reality, it's a risk-filled process that requires detailed procedures, highly trained staff and multiple checks and verification steps in fast-paced environments. A high potential for error combined with a low potential for error detection pose a significant risk to patient safety.

- The traditional manual intravenous drug compounding process has an average error rate of nine percent.[5]
- Seventy-four percent (74%) of manually compounded sterile product errors are undetectable at final product verification and would reach the patient.[6]
- The Pew Charitable Trust's Drug Safety Project identified more than 50 reported compounding errors associated with 1,227 adverse events, including 99 deaths, since 2001.[3]

Contamination

The NECC failures were the result of many missteps, but contamination ranked foremost among them. In addition to employing a pharmacy technician whose license had been revoked and using expired ingredients, NECC was found guilty of not disinfecting the clean rooms where drugs were compounded, routinely ignoring mold and bacteria growth in the clean room environment and failing to properly test drugs before dispensing and shipping.

In testing approximately 17,000 vials prepared for injection into the spines of patients with back pain, the Centers for Disease Control and Prevention identified 18 types of fungi. The resulting fungal meningitis resulted in death, paralysis and long-term hospitalizations for many patients.

Hazardous drug exposure

Compounding pharmacists often work with ingredients considered hazardous by the National Institute for Occupational Safety and Health (NIOSH). NIOSH considers a drug to be hazardous if it exhibits one or more of these characteristics in humans or animals: carcinogenicity, teratogenicity or developmental toxicity, reproductive toxicity, organ toxicity at low doses or genotoxicity. New drugs with structure and toxicity profiles similar to those of existing hazardous drugs (HDs) are assumed to also be hazardous until NIOSH[7] can review them.

More than eight million U.S. healthcare workers are exposed to HDs annually[8] through dermal absorption, mucosal absorption, inhalation, injection or ingestion. Concerns about worker safety began appearing in medical literature as early as the 1960s. Research has linked HD exposure of healthcare workers with acute, short-term reactions, as well as long-term effects, including spontaneous abortion, stillbirths and genetic abnormalities in their children.[9,10]

Without proper precautions, every aspect of handling hazardous drugs – compounding, storage, transport, receiving, dispensing, administering, patient care, spills, disposal and managing waste – can result in exposure.

The evolution of oversight

At the time of the NECC incident, a patchwork of regulations and regulatory bodies oversaw pharmaceutical compounding. Confusion about which body had responsibility left compounding pharmacies without the level of oversight warranted by the complexity and risks of the process.

The USP created minimum standards, but as a non-governmental entity, it had no power to enforce them. Enforcement fell to state boards of pharmacy, but at the time, only 26 states required compounders to meet USP or equivalent quality standards for sterile compounding.[11] Because the FDA had jurisdiction over manufacturers of commercial products and not over compounding pharmacies, it was unable to take action against NECC or any other non-USP-compliant compounder.

One of the immediate responses to the NECC case was the FDA's implementation of the Compounding Quality Act, Title I of the Drug Quality and Security Act (DQSA), in November 2013. The act required all traditional compounding pharmacies – including health system pharmacies – to comply with the standards laid out in USP's general chapters <795>, <797> and <800>.

Today, the USP, government and industry are evolving and integrating their efforts to provide a level of oversight commensurate with the growth, importance and impact of pharmaceutical compounding.

Updates to the USP

The USP Convention is the not-for-profit, science-driven organization that sets standards for the identity, strength, quality and purity of medicine and publishes the U.S. Pharmacopeia. Three chapters that govern pharmacy compounding and hazardous drugs became official on November 1, 2023.

- **USP general chapter <795>, "Pharmaceutical Compounding – Nonsterile Preparations"** describes requirements for the compounding process, facilities, equipment, components, documentation, quality control and training. The chapter is being reorganized and revised to expand guidance for assigning beyond-use dates for compounded nonsterile preparations in the absence of stability information.
- **USP general chapter <797>, "Pharmaceutical Compounding – Sterile Preparations"** describes a number of requirements, including responsibilities of compounding personnel, training, facilities, environmental monitoring and storage and testing of finished preparations. Major revisions affect facility design, environmental controls, storage time of compounded preparations, training and evaluation of compounding personnel, need for automation or workflow technology, and quality assurance requirements.
- **USP general chapter <800>, "Hazardous Drugs – Handling in Healthcare Settings"** provides standards for safe handling of hazardous drugs to minimize the risk of exposure to healthcare personnel, patients and the environment. It describes the responsibilities of personnel who handle hazardous drugs, facility and engineering controls; procedures for deactivating, decontaminating and cleaning, spill control and documentation. These standards apply to all healthcare personnel who receive, prepare, administer, transport or otherwise come in contact with hazardous drugs and all the environments in which they are handled.
- In addition, USP created a new general chapter, **USP <825> "Compounding Radiopharmaceuticals,"** based on recommendations from the Society of Nuclear Medicine and Molecular Imaging's Committee on Radiopharmaceuticals.[11] The new chapter updates and expands standards previously found in USP <797>.

More clarity from the FDA: In its 2018 Compounding Policy Priorities Plan, the FDA outlines the interrelated elements taking shape in response to the NECC case: " ... more powerful oversight of compounders, close federal and state collaboration and a clear legal framework that would provide for compounding to meet patients' medical needs, while also providing the FDA with tools to address unlawful practices that threaten public health."[15]

The plan lays out how the FDA will address quality standards for outsourcing facilities, regulate compounding from bulk drug substances, restrict compounding of drugs that are essentially copies of FDA-approved drugs; solidify the FDA's collaboration with state regulatory authorities and provide guidance on other compounder activities. These initiatives build on FDA efforts already underway, including:

- **Defining two types of compounding pharmacies.** In the DQSA, the FDA created a new section 503B under the U.S. Federal Food, Drug and Cosmetics Act that allows large compounding pharmacies to register as "outsourcing facilities." Traditional compounders continue to be classified under section 503A.
- **503A compounding pharmacies** compound according to prescriptions for specific individual patients for home use and aren't allowed to compound large batches. State boards of pharmacy require them to comply with USP and other guidelines.
- **503B compounding pharmacies** can manufacture large batches with or without prescriptions to be sold to healthcare facilities for office use only. They must comply with USP and other guidelines; validate every process according to the FDA's current good manufacturing practice regulations; submit multiple batches for testing and stability before bringing a new product to market; vet all raw-material suppliers and vendors and conduct regular, rigorous quality inspections.
- **Creating new standards for outsourcing facilities.** Until the FDA established the 503B classification, larger compounding pharmacies making large batches were treated no differently than small compounders operating independently or inside a healthcare facility. The new regulations try to mitigate some of the risks of widespread adverse events by holding large compounding "outsourcing facilities" to standards similar to those required of manufacturers of FDA-regulated pharmaceuticals.

Table 1 provides a side-by-side comparison of regulatory requirements governing 503A and 503B facilities.

503A regulations and guidelines	503B regulations ang guidelines
• Must comply with USP general chapters <795> and <797> and state board of pharmacy regulations • Must perform environmental monitoring every six months • May assign beyond-use dating based on internal or external scientific literature showing stability	• Must comply with USP general chapters <795> and <797>, state board of pharmacy regulations, and 21 Code of Federal Regulations parts 210 and 211 (current good manufacturing practice) • Must develop and conduct an environmental monitoring program that mandates, at minimum, per-production-shift measurement in the ISO five primary compounding areas and weekly measurement in the ISO seven and ISO eight secondary compounding areas • Must maintain a quality department independent of operations and sales with complete autonomy for investigating and releasing product • Must register with each state board of pharmacy, the Drug Enforcement Administration and the FDA, and report its product list to the FDA twice a year

Derived from FDA Group[16]

- **Conducting more aggressive inspections**. Since enactment of the DQSA, the FDA has stepped up its checks of compounding pharmacies – conducting nearly 500 inspections. As a result, the FDA issued more than 180 warning letters advising compounders of significant federal violations and more than 70 letters referring findings to state regulatory agencies. In addition, the agency oversaw more than 150 recalls involving compounded drugs and has worked with the Department of Justice on multiple civil and criminal enforcement actions.[15]

Stronger state boards of pharmacy and Medicare conditions

States remain the primary overseers of traditional, 503A compounders of patient-specific drugs, including community pharmacies, hospital pharmacies and physicians who create medications for administration to their patients.[11] All state boards of pharmacy require traditional pharmacies that compound sterile drugs to be in full compliance with USP <797> and USP <800> or stronger standards.

To help close any gaps in state oversight, the Centers for Medicare & Medicaid Services (CMS) updated its pharmaceutical and nursing conditions of participation to bring them into alignment with USP and other standards of practice.

The additional conditions state that compounding pharmacies must follow “accepted professional principles, including compliance with applicable federal and state laws, regulations and guidelines governing pharmaceutical services, as well as standards or recommendations promoted by nationally recognized professional organizations, such as those found in the U.S. Pharmacopeia/National Formulary.”[17]

CMS has trained its surveyors on sterile compounding standards. Anecdotally, surveyors appear to be taking the new requirements seriously, observing staff for compliance and posing detailed questions regarding storage, documentation and disposition of compounded drugs. CMS also added compliance with the USP compounding chapters to both their pharmaceutical services and nursing services conditions of participation.

Action by accrediting bodies

Accrediting organizations with deemed status to survey on behalf of CMS have added USP best practices to their standards. For example, The Joint Commission now includes direct observation of the compounding of sterile preparations in its survey and has trained surveyors on USP compounding standards. Additionally, it launched a medication compounding certification and added a medication compounding chapter to its home care standards manual.

Both accreditation and eligibility for Medicare and Medicaid funding now require compliance with the USP standards in every state.

How health systems are preparing

Updates to USP <800> and <797> require changes in facilities, equipment and personnel that carry significant staffing and cost implications for health systems. Most pharmacy leaders have been preparing for years, and many have made substantial progress. As they worked to close the gap between previous practice and current compliance, several areas have emerged as the most challenging.

Facility design

Some of the mandated containment strategies require capital investments to ensure that the compounding and storage of HDs occurs in a negative-pressure, externally vented environment. Depending on a health system's current situation, compliance may require the purchase of new equipment, updating of heating, ventilation and air conditioning systems, renovation of compounding suites or construction of new dedicated space. Estimates of startup costs for a clean room installation begin at $150 per square foot, but actual costs may be much higher.[19]

Drug transfer

USP <800> mandates the use of closed-system drug transfer devices for the administration of HDs and recommends them for HD compounding. The cost of implementing these devices will be a significant addition to nursing and pharmacy budgets.

Garb and equipment

Purchasing personal protective equipment is another ongoing expense. Gloves and gowns used must be of a grade that's approved by the American Society for Testing and Materials to prevent penetration of chemotherapy drugs onto clothing or skin. The requirement for more frequent respirator-fit testing for employees who handle HDs will raise respiratory expenditures.

Quality assurance

Medical surveillance, wipe sampling and other required quality assurance activities will add to equipment and personnel costs. Environmental wipe sampling for HD surface contamination costs around $1,500 to $2,000 per six-sample kit and should be performed every six months.[20]

Leadership

USP <800> requires organizations to name a "designated person" responsible for adherence. Because the standards affect a wide range of personnel and locations, this individual could be a pharmacist, nurse, pharmacy technician, quality assurance employee or physician. Organizations must provide sufficient funding, training, support and authority for the designee to enforce standards consistently and hold staff accountable.

Conclusion

Pharmaceutical compounding will remain a critical component of pharmacy operations across the care continuum. In addition to filling dosage and strength gaps in commercially available medications, compounding plays a vital role in personalized medicine, pharmacogenomics, home healthcare and hospice care. And compounding may be the only option when commercial drugs are orphaned, discontinued or in short supply.

The importance of compounded medications makes the updated regulations inevitable and worthwhile. Health systems recognize that the changes and expenditures they are making now are vital to protecting patients and staff. Leading health systems understand that investing in safe compounding practices is simply part of the cost of operating a pharmacy, and they are:

- Developing action plans to comply with compounding standards as well as providing the executive leadership, financing and employee education required to systemize compliance across the organization
- Identifying and remedying potential problems instead of waiting for an adverse event or a visit from a regulatory agency

Vizient resources

Tighter regulation of the pharmaceutical compounding industry is here to stay. Although requirements may vary from state to state, federal regulations require increased protection for patients and healthcare workers is clear. As providers invest in patient and worker safety, Vizient® has invested in solutions and support that advance quality goals and demystify the ever-changing regulatory environment.

Contracted products and services

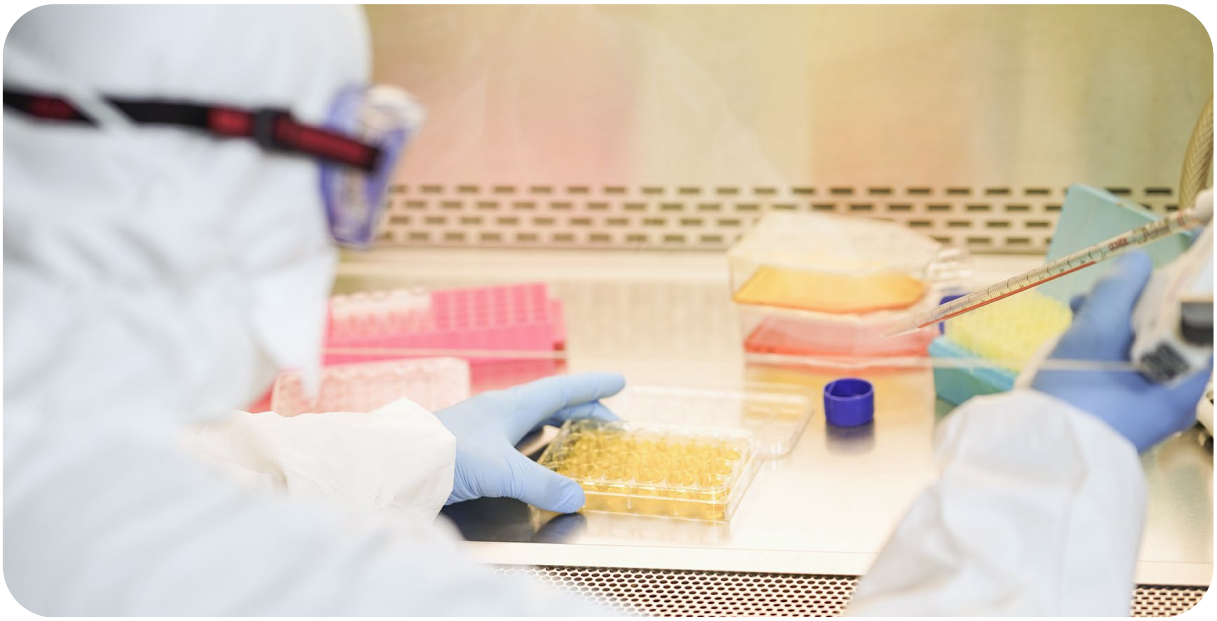
Compliance is critical – and costly. Vizient contracts cover nearly all of the services, equipment and supplies health systems need to upgrade their facilities or build from scratch and to protect their employees, including clean room construction, workflow systems, cleaning supplies and more. For information about Vizient contracts that can help reduce the costs of compliance with drug compounding standards, visit www.vizientinc.com/drugcompounding.

Education and consulting resources

Because compounding regulations are complex and evolving, Vizient provides ongoing education to ensure that healthcare leaders understand trends, expectations and best practices. The Vizient practical pharmacy sterile compounding training on-demand program provides the most up-to-date information on USP sterile compounding of hazardous and non-hazardous drugs. The program can be used for both pharmacists and pharmacy technicians to train new employees and for annual competency confirmation.

Additionally, our expert consultants can evaluate and provide a customized assessment of your USP <795>, <797> and <800> compounding services. We will provide a gap analysis of your current nonsterile, sterile, and hazardous medication compounding environments, safeguards, documentation and practices.

Contact pharmacyquestions@vizientinc.com to learn more.



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