Sterile Compounding Needs Risk Management: Access, Reconstitution Or Preparation, and Administration

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Introduction

Whether in an institutional or clinical setting, a large group practice or pharmacy, or a collaborative practice, there are increasing implications for legal risks to medical executive committees or P&T committees for duties executed while delivering services to patients. Although there are many, one current area for risk management attention is compounding, which also includes hazardous drugs (HDs) and their administration. Since 2012 and in late 2018, new credentialing, regulatory, and related legal aspects in compounding, including use of sterile products and handling of HDs, will require planning to achieve compliance.

By year’s end, effective management and personnel training that address sterile compounding and the administration and handling of HDs need to be employed. Many licensed health professionals and staff are already accountable; however, greater exposure will follow with the implementation of newer harmonized United States Pharmacopeia Convention (USP) standards for infusions, injections, and immunizations. As an organization, if not already being fully addressed, this becomes an important issue for accreditation that oversight committees and organizational leadership must address. This column provides insights into the areas of organizational risk, including regulatory or legal exposure, along with the need for action in select areas of patient care involving the use of sterile products, such as chemotherapy, immunotherapy, ophthalmics, and other routine medical care products.

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National Tragedy Blurs Compliance Approaches

In September 2012, headlines erupted that the New England Compounding Center (NECC)—a compounding pharmacy—had distributed thousands of injectable dosage forms into interstate commerce that were microbially contaminated, leading to an outbreak of fungal meningitis.1-3 NECC was licensed as a retail pharmacy, but took advantage of: 1) critical shortages of much-needed injectable corticosteroids unavailable from Food and Drug Administration (FDA)-regulated manufacturers,6 and 2) court-imposed limitations on the FDA’s authority to restrict the activities of state-licensed pharmacies.7

Congressional hearings brought to light the disconnect between the FDA’s power to oversee what has traditionally been viewed as a part of pharmacy practice—compounding patient prescription medications—and the expanded practices occurring at facilities such as NECC, manufacturing medications for resale.8,9 The passage of the Drug Quality and Security Act (DQSA) in 2013 was in response to the patient safety concerns identified by the FDA and the ability of the FDA to monitor pharmacies that were compounding non-patient-specific medications.8

In response to the NECC tragedy, state boards of pharmacy across the country began reviewing their own oversight and authority over the compounding practices that affect the public safety and welfare of patients.10-15 In the process, the spotlight of attention gradually expanded beyond retail compounding pharmacies to encompass any venue that performed drug compounding, including hospitals, physician practices, infusion companies, and even veterinary facilities.

Regulations and Standards in Flux

Sterile compounding by health professionals is inseparable from patient care. State professional boards, the FDA, accreditation bodies, and payers are seeking the optimal balance between standards and regulatory compliance, and patient access to vitally needed drug compounds that must be prepared by pharmacists, physicians, and nurses.

A cornerstone of the practice of several medical specialties is the acquisition, storage, reconstitution, and administration of a wide array of disease-specific drugs. The business models for medical oncology, gastroenterology, rheumatology, and allergy/immunology are largely dependent on adequate reimbursement.
for the preparation and administration of sterile drugs. In most states, sterile injections and infusions are delivered under the auspices of the physician's medical license, but the privileges and responsibilities of medical licenses vary widely from state to state. The supervising physician is rarely the person who prepares the compounded sterile preparations (CSPs) in medical practices. Instead, the predominant care model is that the drugs are prepared and administered by nurses whose focus may be on the patient’s blood work, whether the drugs are appropriate to the diagnosis, or whether the dose seems appropriate to the condition, rather than the pharmaceutical calculations or the aseptic technique used in the mechanical preparation of the dosage form or the need for a double-check of the finished CSP.

Inpatient care depends on hospital pharmacy personnel compounding a broad array of sterile preparations, including antimicrobials, analgesics, antiemetics, hydration fluids, parenteral nutrition, and antineoplastics. Pharmacies in larger hospitals often prepare thousands of CSPs per week, which are then delivered to patient care units and stored until needed.10

The home infusion pharmacy model provides cost-avoidance for the health care system by allowing for the timely discharge of patients for whom the only remaining continuing therapeutic requirement is the infusion of CSPs. In the home infusion model, the CSPs are prepared in a fully functional cleanroom environment, then delivered to the patients’ homes for administration by the patient or a lay caregiver trained by home health nurses in relevant aseptic techniques.17

State Regulations Must Cover the Entire Spectrum

The requirements for technical sophistication in sterile compounding range from the very simple to the exceedingly complex. A simple process, for example, is using aseptic technique to snap together a manufactured vial of antibiotic powder with a closure that is customized to fit and seal with a corresponding collar on a bag of fluid diluent. A sophisticated process may entail an operator weighing, dissolving, and diluting nonsterile powders to a precisely calculated final concentration, buffering it to a narrow range of pH, then sterilizing the final solution before it is administered into delicate biological spaces, such as the cerebrospinal fluid or the vitreous humor.

State regulatory boards are challenged to write regulations that include both ends of this wide spectrum. Effective state regulations must require adequately trained staff and quality assurance programs that ensure competency at the level of sophistication required to create safe and effective CSPs for patients. Due to the need for readily available national standards, USP established templates for compounding.

USP Compounding Chapters And State Jurisdiction

Chapter <795>, “Pharmaceutical Compounding—Nonsterile Preparations,” was written in 2000. Chapter <797>, “Pharmaceutical Compounding—Sterile Preparations” was first written in 2004 and successfully revised in 2008. These chapters were an existing, exhaustive attempt to document and detail best practices in compounding by health care professionals.

In February 2016, USP published Chapter <800>, “Hazardous Drugs—Handling in Health Care Settings.” Although USP chapters typically become official six months after publication, there was a long delay built into <800> between publication and its becoming “official.” It was initially slated to become official on July 1, 2018, but it is in disharmony with the current version of <797>. USP proposed a revision to <797> in September 2015 to bring the two chapters into harmony, but this version was abandoned after stakeholder comments were evaluated. The USP’s new projected schedule calls for a new <797> revision to be published in September or October of 2018 with an official date of December 1, 2019, and an unaltered <800> to become official on December 1.13

USP is recognized by federal law as one of the national compendia of the scientific attributes of drug substances, but there is no such federal codification for the USP standards for compounding and handling. Drug substances may be deemed adulterated and misbranded if they fail to meet USP’s standards for strength, quality, and purity. Chapters <795>, <797>, and <800> address standards for compounding and handling hazardous drugs, which are part of the practices of pharmacy. These standards are not enforceable by the FDA unless referenced in a regulation or guidance by the FDA. However, the Joint Commission has standards for CSPs that are congruent with these chapters for hospitals and home care organizations. As of January 1, 2018, the Joint Commission’s medication compounding performance standard for home care organizations (MC 01.01.01) requires leadership to assure that quality standards as recognized in USP <795>, <797>, and <800> are implemented in their organizations.19

While the practice of compounding is generally within state pharmacy practice acts, many state pharmacy boards lacked the expertise to write their own standards for sterile compounding and lacked the necessary resources to update the regulations as needed. To address the significant challenges associated with compounding and to protect public safety, many pharmacy boards have begun referencing USP <795>, <797>, and <800> in their state regulations. Some states require all pharmacies compounding sterile products to register with the board of pharmacy. Other states have exemptions for some practitioners, such as hematologists, oncologists, and neurologists. The reference of USP standards in regulations converts the “legal enforceability” of such chapters to reality. Some state pharmacy boards have imposed fines, suspensions, revocations of licensure, or “cease orders” over violations of USP <797>.

Personnel Training And Competency

Whether state professional boards write their own regulations or incorporate USP chapters into rules by reference, there are increasing regulatory requirements regarding training and competency tracking. Most states require that training be completed and competency demonstrated before an operator is permitted to begin preparing sterile compounds for patient administration. Most also require that the organization have a continuous quality assurance program that audits the facility process, product integrity, and educational activities of the staff. These programs are included in the audit by state boards of pharmacy.
Training

USP <797> recommends that sterile compounding operators receive training from “expert personnel and through audio–video instructional sources and professional publications in the theoretical principles and practical skills of aseptic manipulations and in achieving and maintaining ISO class 5 environmental conditions before they begin to prepare CSPs.” It states that operators “shall perform didactic review and pass written and media-fill testing of aseptic manipulative skills initially” and regularly thereafter, the frequency depending on how sophisticated the process is.

Oncology or immunology practices and centers must address new performance payment reform programs through Medicare and some private insurers, which create incentives to transform practice operations. A key aspect to these transformations is to utilize staff to the top of their skill set, which may cause practices to consider whether using allied medical personnel, who are appropriately trained for the detailed processes of drug compounding and mixing, could be more efficient and cost-effective than using specialty certified nurses.

Boards of pharmacy have begun to address training in their regulations. Michigan requires that sterile compounding pharmacies be accredited to validate compliance with USP <797>. Other states have begun requiring continuing education for compounding pharmacists; Massachusetts requires five hours, while Texas requires four hours of training. To meet the increased demand for specialized training in sterile compounding, the Joint Commission has developed a certificate program. This program has been accepted by Michigan for its credentialing requirement. The Pharmacy Technician Certification Board has also launched a sterile compounding certification program for technicians.

In 2015, the Centers for Medicare and Medicaid Services informed state survey agency directors that the conditions for participation in their programs had been updated to include language on the accepted requirements for CSPs prepared outside of the pharmacy. Policies must be developed to address immediate-use CSPs and emergency situations in which these CSPs are prepared outside of the pharmacy. Nursing staff preparing immediate-use CSPs must be trained both in preparation and in beyond-use-date methodology. Because ancillary personnel are key to compounding in many facilities, their training is also essential.

Competency

Competency is usually demonstrated by “gloved fingertip sampling” and growth media transfers. Gloved fingertip sampling is done to demonstrate that, at the completion of the routine hand hygiene–gowning–garbing procedure, the operator can don a pair of sterile gloves without contaminating the fingertips. USP <797> and good manufacturing practices both suggest that the number and variety of media transfers should mimic the most challenging and difficult conditions the operator is qualified to perform as closely as possible.

When an operator’s gloved fingertip sampling or media transfers result in microbial growth, many state rules require that the operator be reassigned until retraining is completed, and he or she has completed a successful no-growth challenge.

With the official date for <800> growing nearer, organizations will likely be expected to develop operator training programs and competency demonstrations for execution of spill cleanups, containment of substances within containment primary engineering controls, appropriate use of closed-system transfer devices, wipe sampling for hazardous drugs, and other routine processes.

Compliance by Discipline

There are pressing reasons for health care facilities to review the roles of personnel and their training and competency, in addition to reviewing their facilities for compliance with the standards used in pharmacy. Since the DQSA was passed by Congress, the FDA has written some guidance and worked with states to monitor and enforce quality standards in compounding. The agency has conducted 500 inspections, resulting in more than 180 warning letters identifying significant violations and more than 70 letters referring inspectional findings to state regulatory agencies. In addition, the FDA has overseen more than 150 recalls involving compounded drugs and has worked with the Department of Justice on multiple civil and criminal enforcement actions.

The FDA has stated that compliance with the DQSA is a top priority for the agency. Its 2018 agenda includes the issuance of guidance documents and proposed and final regulations. A key initiative will be the proposed regulations on cGMP requirements that outsourcing facilities must meet, as well as revised draft guidance to allow a flexible, risk-based approach in meeting these requirements. The FDA is using this new approach to encourage the registration of 503B facilities by making the process and cost manageable for smaller facilities.

Some state legislatures have already passed legislation mandating safe handling regulations to be effective in 2018, far in advance of the finalization of references like USP <797> and <800> (e.g., the New Jersey Hazardous Drug Safe Handling Act and California’s AB 1202—Occupational Exposure to Anti-Neoplastic Drugs).

Compliance for accreditation and safety are two of the main reasons for institutional focus on USP <797> and <795>. However, another major concern should be the increased federal focus on identifying and prosecuting fraud related to compounded medications. From 2006 to 2015, Medicare Part D spending for compounded medications rose from $70 million to $508 million, with $224 million attributed to topical prescriptions. The Office of Inspector General noted this significant increase and declared it a significant issue. The Medicare Fraud Strike Force (MFSF), established in 2007, operates in nine areas of the country. In 2016, its work resulted in criminal and civil charges against 301 individuals and entities for False Claims Act (FCA) and Anti-Kickback Statute (AKS) violations. In 2017, the MFSF conducted its largest enforcement action, which included a Louisiana pharmacist who submitted false and fraudulent claims for $192 million for False Claims Act (FCA) and Anti-Kickback Statute (AKS) violations. In November 2017, the last of eight individuals pled guilty to a $100 million scheme involving false and fraudulent claims for compounded. FCA and AKS violations carry heavy financial penalties, and convictions can result in mandatory exclusion from participation in any federally funded health care program.
Conclusion

Based on this rapidly changing landscape in sterile products, what issues need to be addressed by P&T committees and other leaders? No matter the personnel title or site of care, patient care centers of all sizes need to prepare and train all mixing personnel to understand what they must do, why they must do it, and the necessary decision-making hierarchy for real-world action regarding access, preparation, and administration of sterile products. This becomes a collaborative framework that sets the stage for the implementation of appropriate risk management strategies regardless of how and where nurses, pharmacists, or allied technical personnel are employed. Training and regular competency testing must be consistent, even in large institutional clinical settings. The tracking of training and testing skills also must be consistent. Commonly accepted training and competency standards appropriate for any health care setting are available and should be utilized effectively within the risk management plan.

USP <797> addresses competency and testing, while <800> addresses safe handling for the protection of workers and all others in the organization—they are both a part of this conversation. Although there are elements of these chapters likely to be challenged, other sections related to training and competency serve as good guidestones.

Health care facilities should set forth minimum expectations and guidance for hiring, training, testing, and retesting. Efficient sterile compounding management should balance the need for laser precision in the mixing process against other personnel needs. It can take four to six weeks of intense training for staff to exhibit the proper understanding, rigor, and logic before they are qualified to mix even one preparation for patient use. With the combination of accreditation standards, regulation, and legislation in force today, it is no longer reasonable for sterile product preparation or administration to be learned only while training on the job.

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REFERENCES


