Director's Forum

Ensuring the Safety of Sterile Admixtures Prepared Outside of the Institution

Matthew W. Eberts, PharmD, MBA*; David A. Cecere, PharmD, MBA†;
and Scott Mark, PharmD, MS, MEd, MPH, MBA‡

Director's Forum is designed to guide pharmacy leaders in establishing patient-centered services in hospitals and health systems. This article provides an overview of outsourcing sterile products and discusses tools that pharmacy leaders can use to ensure the safety of the medications dispensed in their institution.

The multi-state fungal meningitis outbreak linked to steroid injections that was first reported in October 2012 resulted in 620 total cases and 39 deaths in 19 states.¹ It placed a spotlight on medication preparation, specifically compounded sterile medications prepared and distributed by third parties. Pharmacy leaders around the country were put in the position of evaluating the suppliers they used to serve their patients. Unfortunately, this was not an isolated incident. Since 1990, there have been 71 compounded products linked to hundreds of adverse events.²

The increase in the number of drug shortages since 2007, as demonstrated in **Figure 1**, further complicated the decision to use outsourced compounded sterile products. In 2011, there were more than 250 drug shortages, of which 183 involved sterile injectable medications.³ As a result, pharmacy leaders needed to expand their supply chain in order to meet the needs of patients. In some cases, this expansion included purchasing sterile products prepared by a third party.

Despite the pressures to deal with drug shortages and other challenges in obtaining and preparing admixed medications, the ultimate charge of pharmacy leaders is to do what is in the best interest of the patients served by their institutions, and a core tenant of that charge is to provide safe medication. However, ensuring that medications are safe is more difficult than ever.

The purpose of this article is to provide an overview of outsourcing sterile products and provide tools pharmacy leaders can use to ensure the safety of the

medications dispensed in their institution. Specifically, this article will discuss background information regarding sterile products prepared outside of the institution by third parties, regulatory issues regarding these products, and best practices for outsourcing prepared sterile products. This article will also provide a list of helpful resources the pharmacy leader can turn to for more detailed information.

NEED TO OUTSOURCE STERILE PRODUCTS

A pharmacy leader may decide to outsource the preparation of certain sterile products for several reasons. One reason is a medication shortage. For instance, morphine 2 mg injectable may not be available to a pharmacy department from its wholesaler or the manufacturer, but a third party admixture pharmacy may be able to compound the product. In most cases, these products are expensive and have a shorter expiration date compared to the traditional product from the manufacturer, but they will allow the pharmacy to continue dispensing critical medications to patients.

Another example might be that the manufactured size or dose of a product does not match how that product is used in practice. The best practice for pharmacy departments is to dispense products in the most ready to use form, and in some cases companies that perform admixture services are able to provide doses in more ready to use sizes. This could mean providing a dose that is less than what the manufacturer provides or providing commonly used injectable medications in syringes such as for operating rooms. These syringes ensure that medications are

*Director of Pharmacy, West Penn Allegheny Health System; †System Director, Pharmaceutical Supply Chain, West Penn Allegheny Health System; ‡Director, Huron Healthcare Consulting Group

Figure 1. National drug shortages: new shortages by year, January 2001 to December 31, 2012. Each column represents the number of new shortages identified during that year. Reproduced, with permission, from the University of Utah Hospitals and Clinics.

properly labeled and that they are drawn up in a sterile environment.

Another advantage to products prepared by third party admixture pharmacies is the beyond-use date requirements. Many health-system pharmacies are not equipped to validate storage longer than the beyond-use dates established by *US Pharmacopeia* (USP) <797>, and limited stability data may be available in the literature. For example, an outsourced product may have a 30-day room temperature beyond-use date for a narcotic infusion that the hospital pharmacy would only give a 48-hour expiration date at room temperature. The longer expiration date allows for storing the product closer to the patient such as in automated dispensing cabinets. By purchasing injectable products with longer expiration dates from compounding pharmacies, health-system pharmacies can reduce IV waste, reduce costs, and decrease human resource requirements.⁴

Other drivers for outsourcing sterile products include limited staffing, technology, or equipment resources. This may be especially true for compounds that require high-risk compounding as defined by USP <797> or require specialized training.

REGULATORY ISSUES

From a regulatory standpoint there are key differences between third party admixture compounding pharmacies depending upon how they are licensed. Pharmacy leaders must recognize these differences if they decide to use an outsourced admixture pharmacy. Third party admixture pharmacies may be registered as drug establishments and/or device manufacturers with the US Food and Drug Administration (FDA). Organizations registered with the FDA as

a drug establishment may apply for National Drug Code (NDC) numbers for their products.⁵ The FDA-registered organizations are able to dispense products in mass quantities without individual patient prescriptions. Of note, if they prepare non-patient-specific controlled substances, they must also be registered with the Drug Enforcement Administration (DEA) as a drug manufacturer. Compounding pharmacies that are registered only in the state they reside can only dispense products upon receipt of an individual patient's prescription. The compounding pharmacy implicated in the meningitis outbreak was not registered with the FDA and therefore was required to only dispense medications for individual patients with prescriptions.

It is paramount that pharmacy leaders investigate how any third party admixture services that they are using are licensed and registered. Once this is known, they must ensure that the practices they have in place with that vendor are appropriate based upon the applicable regulations.

Many professional organizations and individuals have become involved in advocating for updated regulation for companies that prepare sterile admixture products as a third party. They are asking for further clarification regarding the regulation of large-scale compounders that can supply bulk product for health systems versus traditional compounding that dispense based upon patient specific prescriptions.^{2,6} In addition to clarification about the line between manufacturing and compounding, following the meningitis outbreak of 2012 there are calls for clarification on the role of the FDA in terms of regulating and inspecting state licensed compounding pharmacies.² There were legislative proposals in 1997, 2003, and 2007 to give the FDA greater authority over these pharmacies, but the proposals were defeated or overturned on appeal.² To provide clarity, the FDA does have the ability to inspect compounding pharmacies that are not registered with them, as was the case with the compounding pharmacy implicated in the meningitis outbreak, but the overall role and responsibility of the FDA to perform these inspections as well as the level of ability to enforce penalties is still a point of confusion.

In November 2012, the Verifying Authority and Legality in Drug (VALID) Compounding Act was introduced with the aim of strengthening federal regulations for compounding pharmacies. The VALID Compounding Act proposes the following:

1. Preserve state regulatory authority for traditional, small compounding pharmacy activities;

2. Ensure that compounding pharmacies that are operating as drug manufacturers are regulated by the FDA as drug manufacturers;
3. Allow compounding pharmacies with a legitimate reason to compound drugs to request a waiver to enable them to do so before the receipt of a valid prescription;
4. Allow the FDA to waive the requirement to compound drugs solely for individual patients with valid prescriptions in the event of a drug shortage or to protect public health;
5. Allow the FDA to waive the requirement to compound drugs only if they are not copies of commercially available drugs and if doing so is necessary to protect public health or well-being; and
6. Increase transparency to the public by mandating that compounded drugs be labeled to ensure that recipients know that the drugs have not been tested for safety or effectiveness, publishing a "Do Not Compound" list of unsafe or ineffective drugs, and reporting of bad reactions to compounded drugs or any drug that poses a safety risk.

The aim of this legislation is to provide clarity regarding the FDA's role with compounding pharmacies while avoiding the elements that have gotten past legislation struck down by the courts. Reception to this bill has been mixed. In general, pharmacists are supportive of clarifying the FDA's ability to inspect compounding pharmacies and the provisions that pertain to drug shortages, public health, and the "Do Not Compound" list. However there is concern that the legislation may not go far enough in standardizing the classifications between traditional compounding and large-scale compounding.

BEST PRACTICES FOR OUTSOURCED STERILE PRODUCT SERVICES

If a health-system pharmacy department decides that the use of outsourced sterile product admixture will be a part of its supply chain, the department can take steps to best ensure the safety of these products. The pharmacy leader can develop a best practice plan for selecting and providing ongoing quality assurance of compounding pharmacies. The elements for a well-defined outsourced compounding pharmacy assessment plan and an ongoing quality assurance plan are included below. These elements are taken from the American Society of Health-System Pharmacists (ASHP) Foundation's assessment tool.⁷

Initial Assessment

Before selecting an outsourced sterile products service, the pharmacy leader needs to thoroughly validate that company. Even if the health system is already using a compounding pharmacy, it will be worthwhile to perform this assessment on the existing vendors. The first step in the assessment is to ensure that the compounding pharmacy is complying with all regulatory requirements.

Regulatory compliance

The outsourced company must be licensed in the state in which it currently resides and be allowed to ship product into the health-system pharmacy's home state. Additionally, the compounding pharmacy must be compliant with all regulations regarding technician certification, pharmacist to technician ratios, and other state board regulations in the state which it resides. As part of the regulatory assessment, the pharmacy leader should review how the compounding pharmacy is registered (ie, FDA and/or DEA) and whether they are dispensing products in line with that registration. The compounding pharmacy should be able to provide documentation regarding purity and potency of bulk ingredients used for compounding.

Quality and safety measures

The compounding pharmacy should confirm compliance via documentation with USP <797> standards such as media fills, staff competency, cleaning, and physical plant. The sterile admixture pharmacy should perform studies for extended expiration dates using evidence-based and validated testing procedures if no existing expiration date exists. An analysis of the general liability insurance and professional liability insurance of the compounding pharmacy should be reviewed by the health system as well, using the legal department if possible.

Medication safety and product information

The compounding pharmacy should be able to provide information regarding latex, di(2-ethylhexyl) phthalate (DEHP), and any preservatives used in compounding. The pharmacy leader needs to verify that the product provided by the compounding pharmacy is provided in the correct delivery system for that organization (ie, mini-bag, syringe, cassette).

The elements of the assessment listed above are essential when considering a compounding pharmacy for the health system's medication needs. In addition

to this assessment, the pharmacy director should take the following considerations into account:

- If hazardous drugs are involved, determine whether the compounding pharmacy meets National Institute for National Safety and Health (NIOSH), ASHP, and USP <797> guidelines for compounding hazardous drugs.
- Ensure the availability of reports and technical summaries, including beyond-use dating and sterility.
- Determine whether the labeling offered by the compounding pharmacy meets the guidelines for the health system in terms of safety, tamper evident options, and drug name differentiation (eg, tall man lettering).
- Confirm the availability of logistical needs such as ordering process, turnaround time, and Controlled Substance Ordering System (CSOS).
- If possible, perform an on-site review of the compounding pharmacy.

To get the most out of an on-site visit, the pharmacy leader should set the agenda prior to arrival; review all licenses, procedures and policies, staff training materials, cleanliness, and compliance with USP <797>; and observe staff performing admixture processes.⁸

After the selection process is complete, the contract between the health system and compounding pharmacy must be appropriate from a quality assurance and regulatory standpoint. It is advisable to have contracts reviewed by the legal department of the health system. Evergreen or self-renewing clauses in the contract should be avoided. For example, this clause may read that the contract is extended by 1 year at the end of each calendar year automatically. The health system should take a more proactive review of contracted services and ensure that the compounding

pharmacies are meeting the health-systems standards. In the contractual process, the pharmacy leader should be particularly aware of the following:

- The contract should include the types of quality assurance reports that will be made available (ie, sterility testing, staff competencies, USP <797> compliance documents) and how frequently they will be made available.
- Specific quality indicators that will be monitored by the compounding company and shared with the health-system pharmacy should be noted and updated with each contract renewal.
- The contract should include a confidentiality statement for any data or information pertaining to diagnosis, treatment, or health of a patient associated with the health system.
- Conditions for termination of the contract should be outlined.

Ongoing Assessment

Once a compounding pharmacy has been selected, it is critical that the health-system leader remain diligent in holding that compounding pharmacy accountable to the standards put in place by regulatory agencies and the contract that has been executed. One way to help ensure this is to develop policy and procedures to guide the department's interactions with compounding pharmacies. The initial assessment tool should be used to periodically review the compounding pharmacy. The pharmacy leader can also use anecdotal results from what they observe. The pharmacy leader should review the quality assurance reports and make sure they are in line with standards and contractual agreements. If issues are identified on the quality reports, the pharmacy leader should make sure appropriate actions are taken by the compounding

Table 1. Additional resources

Sponsor	Web site	Content
ASHP	http://www.ashp.org/sterilecompounding	Resource center
ISMP	http://www.ismp.org/Tools/compounding.asp	Resources on compounding sterile products
ASHP Foundation	http://www.ashpfoundation.org/SterileProductsTool	Outsourced sterile products preparation: contractor assessment tool
CDC	http://www.cdc.gov/HAI/outbreaks/meningitis.html	Meningitis outbreak investigation
FDA	http://www.fda.gov/Drugs/DrugSafety/FungalMeningitis/ucm325037.htm	Updates about fungal meningitis

Note: ASHP = Association of Health-System Pharmacists; CDC = Centers for Disease Control and Prevention; FDA = US Food and Drug Administration; ISMP = Institute for Safe Medication Practices.

pharmacy. Periodic site visits to the compounding pharmacy using the same criteria as the initial assessment visit will provide another level of oversight.

OUTSOURCED STERILE PRODUCTS RESOURCES

The purpose of this article is to provide the pharmacy leader with an overview of the current state of outsourcing pharmacy admixture and a framework to develop a plan for implementing this service. There are additional resources that offer a greater level of detail; these are periodically updated to provide current information as issues evolve moving forward. The Web sites for those resources are included in **Table 1**. Pharmacy leaders can use these tools to maintain a safe and regulatory complaint supply chain for compounded products.

CONCLUSION

Outsourced sterile admixture companies that prepare compounded products will continue to play a role in the supply chain for many health-system pharmacy departments. This service can provide benefits to the organization, such as additional supply options during shortages and longer beyond-use dates for prepared products. However, it is paramount that the pharmacy leader be diligent to ensure the safety of the products. By using the best practices and resources provided in this article, the pharmacy director can be assured that they have taken steps to monitor the quality of the products dispensed by their department. It is also critical that pharmacy leaders understand and stay current of the regulations impacting this sector of the marketplace. Because of the high visibility of the meningitis outbreak of 2012, pharmacy leaders understand that regulatory visits over the next year, by The Joint Commission, Board of Pharmacy, or their State Department of Health, will be focusing on the use of medications prepared by third party companies and dispensed in the hospital. The pharmacy leader who has a well-developed quality assurance plan; has

performed on-site visits; has current data from their sterile admixture partner, a quality monitoring plan, and appropriately written contracts; and is compliant with local regulations can rest at ease when the inspector asks, "Do you use any outside companies to compound medications?"

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