Drug shortages have become a common problem that threaten to force health systems to ration care or rely on less effective drugs. To deliver necessary drug therapies to their patients, healthcare system pharmacists have turned to outsourced sterile compounding as a means of supplying drugs in short supply. However, outsourced sterile compounded drugs can be a source of contamination and federal oversight of outsourced drug manufacturers has increased to reduce the potential for contamination.

This white paper addresses 503B outsourced sterile compounding operations and outlines considerations for hospitals and pharmacies when selecting outsourced compounding facilities. The purpose of this information is to assist healthcare organizations in the evaluation of outsourcing vendors in the compounding of sterile preparations in order to reduce the potential risk to their healthcare facilities, and protect patients and the public.

**Drug Shortages Create Demand for Compounding**

Hospital pharmacists face daily drug shortages forcing health systems to increase their reliance on in-house and outsourced compounding pharmacies in order to supply needed drugs in short supply. In the first two quarters of 2016, there have been an average of 193 ongoing active drug shortages each month, according to the American Society of Health-System Pharmacists (ASHP). Though the rate of new drug shortages has decreased from a high of 267 in 2011, the shortage of basic drugs still impacts clinicians and patients. Although the number of drugs on the shortage list has decreased over the years, when these items are available, the replacement item is at a very high cost point. Many of these are generic sterile injectable drugs. An interruption in the medical supply chain is a serious problem that can adversely affect drug therapy, compromise or delay medical procedures and result in medication errors, putting patients and the hospital at risk.
Drug shortages also contribute to rising healthcare costs. A 2014 analysis revealed that purchasing costlier generic substitutes for drugs in short supply drove up costs an average of $229.7 million annually.4

Compounding pharmacists play an important role in providing access to specialty drugs and other drugs that are in short supply. Following the fungal meningitis outbreak of 2012 that traced back to a Massachusetts compounding facility and resulted in over 64 deaths, the federal government has increased oversight of compounding pharmacies and compounded sterile preparations (CSPs) with passage of the Drug Quality and Security Act (DQSA), commonly known as the Compounding Quality Act, in November 2013. The law makes a distinction between traditional compounders who work at the neighborhood pharmacy or within the health system they serve and companies producing large quantities of compounded drugs.5

DQSA further defined traditional compounders in section 503A as limited in their scope of drug distribution and generally bound by a “prescription requirement” prior to compounding the drug. Under section 503B, DQSA set up a voluntary category known as an “outsourcing facility” which allows compounders making sterile products to avoid the complex and time-consuming new drug approval requirements and to sell unlimited quantities of drugs on the Federal Drug Administration's (FDA's) drug shortage list without requiring a preexisting prescription anywhere in the country.6
In exchange for this flexibility, compounders must compound under the supervision of a licensed pharmacist or physician, use only drugs from a bulk ingredients list and follow formal current Good Manufacturing Practices (cGMPs). In addition, these compounding facilities are not allowed to compound copies of drugs already on the market unless they are on the FDA’s drug shortage list. They must follow new labeling requirements, report any adverse reactions to the FDA, be inspected by the FDA and pay an annual $15,000 FDA fee.7

In 2014, ASHP published its guidance regarding compounding sterile preparations that discusses at length these federal requirements and the steps compounding sites need to take to be compliant.8 In addition, there are new requirements that need to be considered since the 2014 ASHP document was published that every health system should consider when working with an outsourcing compounding facility. ASHP recommends that each health system determine its own policy on purchasing drugs from compounding pharmacies and on compounding agents in-house. ASHP also recommends that health systems refer to state laws that oversee licensing and distribution of compounded drugs in their state.9 In addition, Comprehensive Pharmacy Services has a policy that states what a health system should consider when selecting a compounder and a process for doing so.

In mid-April 2016, the FDA released three draft guidance documents regarding traditional pharmacy-based compounding by 503A classified facilities and restrictions placed on the distribution of drug products compounded by those organizations. The first draft guidance document defines a “facility” and states that a single location cannot contain both traditional and outsourced compounding operations under the same roof because the two types of facilities are held to different quality standards by the FDA. The second draft guidance clarifies the permissible scope of a traditional hospital and health system compounding facility not registered as a 503B outsourcing facility. And the third document outlines the prescription requirement for compounding performed in a 503A facility.10

Evaluating an Outsourced Compounding Facility

In evaluating an outsourced compounding facility, hospitals and their pharmacies should consider the following:

**REGULATORY COMPLIANCE:**

- Outsourcer should be registered as a drug manufacturer with the FDA as required by DQSA. This requirement, and the payment of the $15,000 fee, is necessary for all 503B facilities as defined by DQSA. In addition, ask if the outsourcer registered as a drug manufacturer with the Drug Enforcement Administration (DEA).
• Outsourcer should have a state pharmacy license in the state where the compounding center resides. State Boards of Pharmacy for Sterile Compounding Practices have their own regulations regarding compounding facilities that must be met, and these regulations may differ from state-to-state. The State Boards are charged with inspecting outsourcers within their states. Also consider if the outsourcer is licensed to ship to the state where the purchasing facility resides. And ask if the outsourcer has had any disciplinary or punitive action filed against them by any regulatory agency within the last 36 months. The FDA provides information on inspection issues, filed warning letters and recalls that can be viewed on this website: Compounding: Inspections, Recalls and Other Actions.¹¹

• All pharmacists working for the outsourcer should be licensed by the state in which they are practicing. Outsourcer should meet or exceed state required pharmacist-to-pharmacy technician ratios for the state where the compounder is located. Pharmacy techs may be required to be licensed by their state board. Ask what percentage of the outsourcer’s pharmacy sterile compounding technician staff are certified by an authoritative board such as the Pharmacy Technician Certification Board.

• If outsourcer deals with hazardous drugs, outsourcer must meet National Institute for Occupational Safety and Health (NIOSH) requirements to ensure that facility personnel are working in a safe environment and to protect from cross contamination with other compounded sterile preparations (CSPs). These requirements typically cover the design and functionality of compounding environments, including the sterile compounding room, ante-room and buffer room. Outsourcer should be able to provide documentation that confirms the International Organization for Standardization (ISO) category of each room, the existence of laminar flow hoods and the number of air exchanges per hour per room. This documentation should be evaluated and updated every 6 months.

• If a commercial product component of a preparation is on backorder, the outsourcer should be able to provide a certificate of analysis (COA), potency testing and proof that all other requirements are met for high-risk level compounding. When no commercial source exists to prepare admixtures, outsourcer must use USP grade bulk ingredients obtained from a cGMP compliant supplier. Outsourcer should be in possession of appropriate COAs and potency testing for all bulk ingredients used from the supplier.

QUALITY AND PATIENT SAFETY

• The outsourcer should have established Standard Operating Procedure documents (SOPs) with step-by-step instructions for all personnel that outlines how specific procedures are performed as well as up-to-date policies and procedures documents. The outsourcer should be able to provide
documentation that confirms that staff competency is evaluated prior to staff compounding actual drug preparations. This includes competency in procedures such as: garbing, hand hygiene, aseptic technique, cleaning and disinfection procedures in compliance with USP chapter <797> guidelines.

- Outsourcer should be able to provide documentation confirming that pharmacists and pharmacy techs are per-qualified using media fills before compounding drug preparations. USP chapter <797> requires that media-fill testing should occur at least every 12 months for personnel who compound low and medium-risk preparations. Testing at least every 6 months is required for personnel involved in compounding high-risk preparations.\textsuperscript{12}

- Outsourcer should be able to verify that staff members comply with glove-tip testing processes that are consistent with USP chapter <797> standards. Three sets of glove fingertip evaluations must be completed with no growth prior to staff being allowed to compound sterile preparations.\textsuperscript{13}

- Outsourcer should show evidence that USP chapter <800> standards are followed. USP <800> expands from Chapter 797 with guidelines to protect both personal and the environment.

- Outsourcer should provide evidence of internal studies that determine extended expiration dates using evidence-based and validated stability testing procedures for CSPs for which no extended expiration evidence exists. Procedures should be in place for determining the Beyond-Use-Date (BUD) of a CSP. Outsourcer should follow evidence-based and validated stability testing procedures to evaluate each preparation for chemical characteristics such as pH, particulate matter, color and sterility, including container closure integrity testing.

- Outsourcer should have documentation of routine surface microbiological and fungal environmental monitoring to minimize contamination. Additionally, outsourcer should have documentation of routine nonviable and viable airborne particle testing in primary engineering controls (e.g., laminar flow workbench, biological safety cabinet) and room air according to USP chapter <797> standards. This testing should occur every 6 months in all compounding areas as part of the compounding recertification process.

- Outsourcer should have documentation of business continuity plans that are in place in the event of a natural or man-made disaster or public health emergency.
STERILITY MAINTENANCE

- Outsourcer should have documentation that cleaning methods and agents are effective in preventing contamination of the sterile preparation area. Sterile alcohol should be used to sanitize vials, ports, gloves and the laminar flow hoods. Each batch should be tested for sterility.
- Outsourcer should have action and alert limits in place for environmental monitoring.
- Outsourcer should have documented processes and procedures to ensure that CSPs leaving the site retain integrity and stability through the shipping process.

LABELING AND PACKAGING

- Outsourcer should use drug name differentiation in the form of TALL MAN lettering as defined by an authoritative body for sound-alike drugs. Labels should contain visual cues to differentiate drug names and drug concentrations within a therapeutic class.
- Labels should provide total drug amount and concentration to ensure administration and correct dose.
- Special requirements should be in place for handling and labeling chemotoxic and other hazardous drugs.
- Label should include bar code that allows visualization of drug name and concentration when used in automated infusion pumps or syringe pumps.
- Packaging should include tamper-evident options such as overwrap, shrink wrap, tamper evident foils and/or tamper-evident caps.

ORDERING

- Outsourcer should provide real-time reporting tool for shipment tracking, order history and invoices. Shipping time-frames should include same-day and next-day delivery options.
- Outsourcer should provide reliable web-based ordering and E-222 “CSOS” ordering for controlled substance purchases.
- Outsourcer should have staff members who are knowledgeable in the necessary clinical pharmacy areas who can ensure that an order received from a hospital is clinically and solution stability appropriate.
- Outsourcer should have secure area with staff identification controls in place when preparing CSPs using controlled substances.
- Outsourcer should have a track record for innovation and process evolution as evidenced by customer testimonials.
- Outsourcer should have a process in place for recalls on batch and individual products.

Hospitals and their pharmacies must do all they can to REDUCE THEIR OWN RISK, protect their PATIENTS and the public in general.
Summary

Going forward, federal oversight as well as state enforcement of existing statues are expected to continue and possibly increase. Health care organizations must take great care with selecting the outsourced compounding facilities they establish a working relationship with. Hospitals and their pharmacies must do all they can to reduce their own risk, protect their patients and the public in general.

ABOUT COMPREHENSIVE PHARMACY SERVICES:

Founded 45 years ago and employing over 2,000 pharmacy professionals, CPS is the nation’s oldest and largest provider of pharmacy support services to more than 600 hospitals and healthcare facilities pharmacies. CPS helps hospital pharmacists tackle complex problems such as medication reconciliation, hyper-inflated drug costs, standardization, centralized distribution, retail pharmacies, compliance, 340B programs and much more, leading to increased quality, reduced admissions and lower costs.

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