Over the past 3 decades, outsourcing sterile compounding pharmacies have become an essential partner for most US hospitals. At one time, most compounded sterile preparations (CSPs) were mixed at the bedside, either by staff nurses or physicians. This was an effective solution in a different era of medicine; however, in the 1980s and 1990s, changes in the US population and advances in medical care led to an increasing need for CSPs. The aging population meant a larger demographic of adults aged 65 and older, with more comorbidities and medication needs. Advances in maternal–fetal medicine yielded improved survival rates for fragile, premature infants, many of whom required total parenteral nutrition (TPN).

This rapid increase in CSP volume put untenable pressure on bedside compounding, leading hospitals to develop their own internal pharmacy-based centralized IV admixture (CIVA) programs. But the growing need for compounded medications soon began to overwhelm the internal capabilities of many hospitals, even those with large in-house pharmacies. Safety and quality standards for CSPs were poorly defined, however, and nosocomial outbreaks and medication errors became common, leading to increased attention and need for safer compounding practices.

Attempts to improve safety in sterile compounding date back to the 1970s, with the establishment of the National Coordinating Committee on Large Volume Parenterals (NCCLVP) by what was then known as the US Pharmacopeial Convention (USP). The NCCLVP was one of the first organizations to develop standards of practice for the preparation, labeling, and quality assurance of compounded products prepared by hospital pharmacies.

The organization dissolved in the 1980s, and over the next 2 decades, a series of attempts were made to establish consistent safety and quality standards for CSPs.
1992: USP issued Chapter <1074>, Dispensing Practices for Sterile Drug Products Intended for Home Use, a draft recommendation aimed at providing practice standards for CSPs. The recommendation was ultimately finalized as Chapter <1200>, Sterile Drug Products for Home Use, although it carried no legal or regulatory authority.2

1993: The American Society of Health-System Pharmacists (ASHP) published a Technical Assistance Bulletin entitled Quality Assurance for Pharmacy-Prepared Sterile Products, which laid out quality assurance measures to be used in the compounding of sterile preparations.3 But follow-up surveys in 1995 and 2002 found that hospital pharmacies largely lacked the necessary controls for their compounding environments.2

1997: The US Food and Drug Administration Modernization Act (FDAMA) was enacted. Section 503A, Pharmacy Compounding, defines legitimate compounding in order to protect patients from harm. The FDA was given the ability to identify certain agents that represented a high risk to public safety.2

2004: USP published Chapter <797>, the first enforceable guidelines for CSPs. State boards of pharmacy, the FDA, and accreditation agencies began using these measures to govern inspections.2,4

2008: USP published revisions to Chapter <797> following cost and resource concerns about the 2004 publication.2 Revisions were made to the sections on environmental and quality control regarding full clean rooms, as well as changes to the sections on sterility, stability, and expiration dates.2,4

Complying with the regulations outlined in USP Chapter <797> became increasingly challenging for many hospitals; institutions needed to dedicate considerable space, staff, and monetary resources to comply with these standards.1 Subsequently, hospitals were forced to adjust their workflow as CSPs had to be prepared by the pharmacy under specific protocol. Pharmacy staff was tasked with mixing more CSPs rather than providing hands-on patient care.1

As a result, many hospitals turned to compounding providers (the term outsourcing was coined) to handle the complexities of preparing CSPs. Moreover, CSPs were required to undergo expensive sterility and stability testing to achieve extended beyond-use dates (BUDs), an important designation to assure quality, improve patient safety, and reduce medication waste. This became especially important with the rise of automated dispensing machines, which allowed rapid and controlled access to CSPs at the point of care rather than waiting for the hospital pharmacy to mix CSPs on demand, with predictably slower turnaround times.3 These factors ultimately led to the rise of “anticipatory compounding”—making limited quantities of compounded medications in preparation for a certain number of expected, although nonspecific, patient orders.

The growing number of compounding pharmacies also offered a much-needed solution to the ongoing drug shortage problem.5 Outside vendors can provide access to discontinued medications or drugs in short supply by compounding the specific drug a hospital pharmacy may not be able to get from any other source, in order to fill a patient’s prescription.

Today, the vast majority of US hospitals have some form of CIVA program, and an April 2013 report from the Department of Health and Human Services Office of Inspector General (HHS OIG) found that 92% of acute-care hospitals use CSPs.6 Moreover, approximately 75% of these hospitals currently outsource at least some of their compounding.6 According to the International Academy of Compounding Pharmacists, of the approximately $300 billion in prescription medications sold annually in the United States, up to 3% are filled by entities considered to be a compounding pharmacy,7 although many of them do not supply to hospitals.

Current Legislation and The Price of Inadequacy

Compounding pharmacies sit in an unusual middle zone when it comes to regulation. They are, technically, subject to oversight by the FDA—in a 1992 Compliance Policy Guide, the FDA stated that compounding pharmacies are not explicitly exempt from its authority.6 But the FDAMA exempted compounding pharmacies from FDA regulation with a few stipulations: They must only compound drugs for individual patients with valid prescriptions; the drugs must be compounded using approved ingredients and standard manufacturing processes; and the drugs may not be copies of other drugs already commercially available.9

Under the patchwork of current law, compounding pharmacies are primarily governed by the state board of pharmacy in their home state, some of which use safe-practice guidelines established in USP Chapter <797> as well as Chapter <795>, Pharmaceutical Compounding—Non-sterile Preparations.10 The National Association of Boards of Pharmacy (NABP) has incorporated USP Chapter <797> into its Model State Pharmacy Act and Model Rules,3 and some states have adopted Chapter <797> in its entirety. However, as of 2013, only 18 states require full compliance with USP Chapter <797>.11

This “one-license-fits-all” regulatory approach means that in order to engage in interstate commerce, anticipatory compounders must be licensed within multiple states, all with varying levels of safety regulations and inspection standards.11 Consequently, hospitals must ensure that the compounding pharmacies they partner with adhere to rigorous quality and safety standards and trust that state boards of pharmacy perform their duties to ensure that quality and process controls are in place.

Unfortunately, irresponsible compounding practices by a small minority of vendors combined with inadequate and inconsistent oversight by state regulators have come to threaten public safety. Nowhere was this threat more apparent than the multistate fungal infection outbreak attributed to contaminated compounded methylprednisolone acetate (MPA), which was distributed by the New England Compounding Center (NECC). The first official case was reported on Sept. 18, 2012, and by Oct. 1, the FDA, Massachusetts Department of Health, and Massachusetts Board of Pharmacy had launched a collaborative investigation of NECC. Problematic conditions observed at the NECC facility included:12

- The use of nonsterile active pharmaceutical ingredients (APIs) and raw materials to formulate injectable suspensions, although formula worksheets stated that raw materials were sterile.
- No documentation or evidence to support the effectiveness of
the steam autoclave cycle used to sterilize suspensions formulated using nonsterile APIs and raw materials.

- Microbial isolates (bacteria and mold) found in multiple locations within the company’s clean rooms.
- Air conditioning in the clean rooms shut off nightly between 8 PM and 5:30 AM.
- Tarnished discoloration and condensation on the interior surfaces of several autoclaves.
- Green and yellow residue on ceiling surfaces, hoods, and other areas of prep and clean rooms.
- A boiler leaking water into soiled puddles within 30 feet of the entrance to a prep room.
- Visibly soiled mats outside clean rooms.

As of July 2013, the NECC outbreak has resulted in 749 confirmed cases and 61 deaths.13 This was the worst tragedy linked to nonsterile practices in pharmaceutical compounding, but it was far from the first. As FDA Commissioner Margaret Hamburg explained in Congressional testimony in April 2013,14 multiple outbreaks of infections and other complications resulting in serious injury and death have been linked to compounded products over the past 20 years,15 including:

- California, 2001: 13 patients were hospitalized and 22 received medical care after injections of a contaminated steroid solution.
- Virginia, 2005: 5 cases of systemic inflammatory response syndrome resulted from the use of a contaminated cardioplegia solution; 3 of those patients died.
- Multiple states, 2007: A Texas compounding pharmacy sold hyper-concentrated doses of an IV solution that were up to 640% higher than the strength listed on the label; 3 people died from multiple organ failure.
- Florida, 2011: About 21 patients developed bacterial eye infections from contaminated intravitreal injections. Several suffered long-term vision loss. Multiple warnings from the FDA about the hazards of compounded intravitreal injections have continued.

Given the devastating consequences of irresponsible compounding practices, it has become more important than ever for hospitals to understand how responsible compounders should operate and how to identify who those responsible compounding partners are.

**The Responsible Outsourced Compounder’s Approach to Safe CSPs**

Inconsistencies in regulatory and safety standards across state lines make it essential for hospitals to ensure that outside sterile compounding vendors are taking the necessary precautions. However, during his keynote address at the Pharmacy Sterile Compounding Summit in February 2013, Gary Kerr, PharmD, Massachusetts Society of Health-System Pharmacists, explained that he and other directors of hospital pharmacy worry about whether they have the necessary expertise and resources to assess external compounding pharmacies.17

At the very least, a responsible compounding pharmacy will adhere to USP Chapters <795> and <797>, whether or not their state board of pharmacy mandates full compliance. Critical elements of USP Chapter <797> include4:

### Compounding Terminology

**Traditional compounding:** Defined by the FDA as “the combining, mixing, or altering of ingredients to create a customized medication for an individual patient in response to a licensed practitioner’s prescription.”14 This may be done to change the drug’s route of administration (eg, from a pill to a liquid for patients who cannot swallow pills), to remove an ingredient that the patient is allergic to, to obtain an optimal dose, or simply to improve flavor or texture. Compounding of this type is most commonly performed in the case of IV/parenteral nutrition.

**“Nontraditional” compounding:** Historically this term has been used to refer to mass production (even if on a smaller scale) of a compounded product, not for the needs of a specific patient. This treads the line between compounding and manufacturing. Entities that compound on an anticipatory basis, providing CSPs for hospitals based on expected need to match the high-volume demands of today’s institutions, also fall under this category. Congress has proposed a new definition for anticipatory compounders: “compounding manufacturers.”

**Compounding manufacturers:** A new definition proposed by Congress to classify entities that compound a sterile drug without a prescription and introduce it into interstate commerce, or repackage a drug using sterile, preservative-free, single-dose vials or by pooling sterile drugs.16

**Nonsterile preparations:** Include creams, ointments, or gels applied to the skin, and pills or capsules taken orally. They are lower-risk products and are subject to less regulatory scrutiny.

**Sterile preparations:** These usually are injected or infused drugs that carry a higher risk for infection and other adverse events. This category includes sterile-to-sterile products, in which a pharmacist constitutes one sterile product from another; and nonsterile-to-sterile products, which require sterilization of the compounded mixture once it has been prepared from one or more nonsterile ingredients. The risk is highest with products that started with a nonsterile component, as observed in the NECC outbreak.
• **Up-to-date Standard Operating Procedures (SOPs):** These include a plan for prevention of microbiologic contamination of sterile preparations, documentation of the validity of these sterile procedures, and written justification. The SOPs also should outline comprehensive procedures for employees, environmental cleaning, and product testing, as well as the frequency of such testing. The manual should be reviewed and updated on a regular basis and be available for inspection by boards of pharmacy, federal regulatory representatives, or hospital pharmacies conducting a site audit of a vendor.

• **At least one structurally isolated area used only for the preparation of sterile pharmaceutical products:** This area must maintain appropriate light, ventilation, temperature, moisture, sanitation, and security levels. It also must be able to accommodate a laminar flow hood.

• **Well-established maintenance schedule:** This must include a system for cleaning and disinfecting all rooms and equipment involved in sterile preparations, and specific processes for cleaning and qualifying laminar flow hoods.

• **Thorough and complete compounding and dispensation records.**

• **Augmented safety procedures for preparing cytotoxic drugs:** This must include a dedicated vertical flow, Class II biological safety cabinet, protective apparel for personnel, written policies and procedures for response to spills of cytotoxic material, and compliance with all applicable laws and regulations of the disposal of such material.

• **Quality assurance program:** This program monitors patient outcomes, adverse events, staff training and development, initial qualifications (particularly training requirements for personnel involved in aseptic manipulations), ongoing staff competency assessments, product integrity, and maintenance of equipment and facilities. Additionally, the program can perform product, employee, and environmental testing. Clean rooms and laminar flow hoods should be examined and certified by an independent inspector at least once every 6 months. The program should have complete documentation available.

• **A comprehensive, well-established training and competency assessment program:** This program ensures that staff understands SOPs and receives routine training and qualification assessments for CSPs and for compliance with SOPs and federal and state regulations.

For compounding pharmacies that engage in bulk compounding of nonsterile-to-sterile preparations—the source of many of the outbreaks and other adverse events—additional precautions must be taken. In particular, the pharmacy should be able to demonstrate that it conducts extensive end-product testing for nonsterile-to-sterile materials, including tests for particulate matter, pyrogens, and microbes. The compounding pharmacy also must take extra steps to validate that the clinical lab performing this quality testing meets federal and state regulations for performance. Importantly, a critical program must be in place to audit suppliers of bulk APIs.

Although much discussion of compounding safety has focused on compliance with USP Chapter <795>, less attention has been paid to Chapter <795>. This section focuses on nonsterile final preparations, and it has important implications about the quality of the product itself. A good compounding pharmacy will pay close attention to Chapter <795>. Among its key elements:

• **Rigorous attention to stability criteria and BUDs, using drug-specific and general stability documentation and literature.** Compounders should assign BUDs conservatively, paying attention to drug-specific and general stability documentation and literature.

• **Use of USP- or national formulary-grade substances whenever possible.**

• **Adherence to principles for compounding products of acceptable strength, quality, and purity:** Requires a review of physical and chemical properties, assessment for possibly unfavorable or allergenic added substances, identification of the quality and quantity of each active ingredient, and confirmation of calculations and measurements.

• **Understanding appropriate methods for compounding various specific formulations of a nonsterile drug:** Includes capsules, powders, lozenges and tablets; emulsions, solutions, and suspensions; suppositories; and creams, topical gels, ointments, and pastes.

There is also another section of USP that applies to pharmaceutical compounding: Chapter <71>. This section sets standards for sterility testing, including appropriate culture media, time of incubation, minimum quantity of product to be used, and appropriate sterility testing methods for each specific type of product that might be made by a compounding pharmacy, such as ointments and creams, prefilled syringes, aqueous solutions, and antibiotic solids.

Compliance with USP Chapters <795>, <797>, and <71> guidelines is essential, but it is not sufficient for good pharmaceutical compounding practice. Truly responsible compounders go beyond these foundational documents to incorporate additional recommendations from entities such as the Institute for Safe Medication Practices (ISMP), the Joint Commission, the Centers for Medicare & Medicaid Services, the ASHP, and other sources of safe medication policies and procedures.

### Institute for Safe Medication Practices

In December 2012, the ISMP issued finalized proceedings from the October 2011 Sterile Preparation Compounding Safety Summit, titled **Guidelines for Safe Preparation of Sterile Compounds.** The resource defers to USP Chapter <797> for standards to ensure the sterility of compounded products; instead, the ISMP document focuses on the prevention of IV admixture errors. Therefore, it does not address topics such as clean room sterility and laminar flow hoods, but rather focuses on areas that include order entry and verification, drug storage and conservation, and technology solutions such as IV workflow software and automated IV compounding devices.

The document’s recommendations are categorized as Level 1: best practices that are strongly encouraged but that may not always be applicable; Level 2: minimum standards of practice; and Level 3: legal and regulatory mandates. Hospitals should...
ensure that compounding providers adhere with all Level 2 and 3 recommendations. Ideally, the compounding pharmacy should adhere with all 3 levels. Pharmacies looking to do business with an outsourced IV compounding pharmacy should also evaluate the potential vendor against Level 1 best practice standards before considering potential contracts.19

The Joint Commission

Although the Joint Commission has yet to publish specific compounding-focused standards, a number of its medication management standards also pertain to compounding pharmacy practices. Responsible compounding pharmacies should comply with Joint Commission recommendations in all relevant areas of medication management.

Beyond adherence to organizational standards and legal and regulatory requirements, hospitals should seek partnerships with compounding vendors that employ innovative packaging, labeling, and technological solutions to help reduce medication errors. Organizations such as the ISMP, the FDA, and the Joint Commission all have endorsed various labeling enhancements.20 Examples of safer packaging and labeling include:

- “Tall Man” lettering to help distinguish sound-alike/look-alike drugs (eg, predniSONE vs prednisolone; buPROPion vs busPIRone). The FDA has an approved list of Tall Man letters, but the ISMP has suggested a more comprehensive list for readily confused drug names (https://www.ismp.org/tools/tallmanletters.pdf), which a proactive compounder also should employ.
- Color-coding to sort preparations by class. For example, prefilled syringes for the OR setting could employ blue labels for opioids, fluorescent red for neuromuscular blockers, yellow for induction agents, orange for sedatives, violet for vasopressors, and green for anticholinergics.
- Unique shapes and symbols to avoid confusion over multiple dosage formulations in the same drug family or class.
- On the technology side, bar-coded labels should be used to help ensure that the right drug at the proper dose is administered to patients. Vendors should offer bar codes that incorporate drug names, lot numbers, and expiration dates, all within a single scan if possible. Figures 1 and 2 depict the types of clear, concise packaging that outsourcing compounding pharmacies can provide.

Finally, the compounding pharmacy’s culture needs to be one of openness, transparency, and commitment to the advancement of quality and safety in pharmaceutical compounding. A responsible compounding pharmacy follows proper licensing procedures with the boards of pharmacy in every state in which it practices; some go as far as registering with the FDA. Site visits not only should be accepted, but also welcomed and encouraged. If errors do occur, or if inspections reveal violations, the compounding pharmacy should employ a full-disclosure policy about these problems and steps it has taken to remedy them, informing customers in a timely fashion.

Figure 1. Distinct labeling for anesthesia syringes in the operating room to help with drug identification. Image courtesy of PharMEDium.
Risks and Burdens of In-House Compounding

Some large hospitals and health systems can absorb the costs and other burdens required for a fully operational in-house compounding pharmacy. The Cleveland Clinic Health System, for example, prepares the majority of its estimated 870,000 annual doses of compounded medications (56% in response to patient-specific orders, 44% prepared in anticipation of need based on previous experience) at its main campus pharmacy, although compounding activities occur at each of its 10 hospitals. But even this large health system outsources some high-risk CSPs, such as pain pump refills, as well as parenteral nutrition and some cardioplegia solutions. Inevitably, all institutions face considerable obstacles and risks related to performing all of their compounding internally.

Training and Education

Hospitals, and many hospital pharmacists, are not necessarily leading experts in IV sterile compounding processes and procedures. Although the basics of compounding are taught in pharmacy school curricula, the level of this instruction varies widely. A 2007 survey of US pharmacy schools found that although all schools offered some form of instruction in CSPs, only 21% offered a standalone course on the subject. Although 88% of schools taught students about USP Chapter <797> standards for sterile compounding, only 13% of pharmacy school deans felt this CSP training was adequate.

Moreover, training and educating staff about USP Chapter <797> compliance remains challenging to in-hospital compounding. The 2012 USP Chapter <797> Compliance Survey found that 19% of respondents (77 of 419) cited a scarcity of training and competency resources to help educate staff as the greatest challenge in compliance. Similarly, 20% of respondents (81 of 419) cited the time required to implement Chapter <797> changes as an obstacle to compliance.

Medication Errors

In some cases, it has been found that medication errors may be more likely to occur when hospitals make their own sterile preparations without the proper facilities, training, or staff. For example, preparing syringes at the point of care has been linked with an increased rate of errors, with particular hazards linked to the use of unlabeled syringes.

Purchasing prefilled syringes from a high-quality compounding pharmacy may help reduce these errors. Recently, physicians at Barnes-Jewish Hospital in St. Louis, Missouri, standardized anesthesia medication trays for their operating rooms (ORs) using such prefilled syringes from an outsourced entity. They found that medication management significantly improved, with inclusion of medication concentration on the label increasing from 31% at baseline to 78% post intervention ($P<0.001$).

Labeling and Distribution

Ensuring that medication labels accurately display the drug and concentration on each preparation may be difficult for hospital pharmacies, particularly those without a robust admixture program. Moreover, providing clear, easy-to-read labels is vital to reduce the risk for medication errors, particularly in the OR and ICU.
Compounding vendors can provide innovative labeling, such as bar coding, Tall Man lettering, and the use of shapes on the labels for ease of selection among medications in the same therapeutic class (Figure 3). Syringes may include color-coded labels based on drug class, as well as drug names displayed on circumferential bands with graduated marks to aid clinicians during medication administration.

**Dating, Testing, and Waste**

Unless the hospital pharmacy has a comprehensive quality and testing program, most in-house sterile compounded medications have a shorter shelf life, which leaves the hospital more vulnerable to waste resulting from preparations that go unused and must be discarded. Current USP requirements mandate that CSPs can only be dated for the length of time outlined in the USP chapters based on the risk level of the preparation, or what information is in the published literature, which means that the hospital pharmacy must conduct multiple runs to make their IV preparations on both the day and night shifts.

Outsourcers, by contrast, have BUD parameters that better match the ebb and flow of a hospital’s drug supply needs. Responsible outside vendors have the capability to conduct extensive testing that uses a stability-indicating method (a validated, quantitative analytical procedure that measures the amount of API free from potential interferences) to provide data to support extended BUDs for the same compounds. This testing ensures quality and significantly improves the shelf life of CSPs, thus reducing waste. If a patient is discharged or an order is changed, the extended dating allows the product to be reused. For hospitals with pharmacies that do not operate 24 hours a day, outsourcing ready-to-use CSPs with extended shelf lives is even more important. The medication waste resulting from limited expiration dates that apply to a hospital’s in-house pharmacy can be significant. Research in an OR setting suggests that BUDs provided by outsourced compounders, in conjunction with tamper-evident packaging, can reduce drug waste by up to 61%.

**Physical and Opportunity Costs**

Equipping an in-house hospital compounding pharmacy that is fully compliant with all relevant USP chapters also can be expensive considering the requirements for clean rooms,
negative pressure rooms, storage for hazardous drugs, laminar flow hoods, isolators, and other high-cost capital expenditures. A single chemotherapy hood, for example, could cost more than $40,000—a substantial expenditure for any hospital. According to the HHS OIG survey, only 56% of hospitals surveyed had a USP Chapter <797>–compliant clean room.6

At virtually every hospital, there is competition for the scarce resources allotted to capital projects. Even if there might be a budget for such an investment, the facilities needed for compounding sterile preparations have a significant footprint, and space is often at a premium, particularly in community hospitals. In-hospital compounding also imposes a considerable opportunity cost for hospitals. Preparation and dispensing time impede pharmacists and other staff from providing hands-on clinical services to patients. This opportunity cost is not ideal considering the fact that many hospitals have implemented patient-focused care initiatives. In fact, the ASHP Pharmacy Practice Model Initiative has urged hospitals and other health care institutions to incorporate pharmacists in all aspects of medication management and related patient counseling.27

Compliance

Recent analyses of hospitals’ capabilities to move compounding back in-house have underscored the effect of all of these limitations (Table 1).6,22 The inaugural USP Compliance Survey was conducted in 2011 and was repeated in 2012, with hospital pharmacies representing the vast majority of survey respondents. "Despite the incremental improvements in a few of the key chapter requirements, there continue to be many opportunities to achieve improved compliance with the chapter," the study directors wrote in their published analysis.22 Respondents achieved USP Chapter <797>–compliance scores of 80% or higher in a number of areas, including inventory storage and handling of CSPs, depyrogenation by dry heat, aseptic technique, and temperature and humidity monitoring; however, compliance scores of 70% or lower were reported in many areas.22 These included surface sampling, airflow and differential pressure monitoring, sterility testing, and bacterial endotoxin testing. For example, in 2012 only 53% of hospitals had a current, written environmental sampling plan that documents where viable air sampling and surface sampling occurs within the controlled environments—a very small improvement over 2011, when 49% had such plans.22

In sum, hospitals face a variety of considerable obstacles and burdens in performing in-house compounding. As a result, the HHS OIG report found that approximately 75% of US hospitals outsource at least some of their sterile compounding needs.6 Outsourcing has become an even more important resource in the current environment of persistent drug shortages. In fact, hospitals that outsource at least some of their CSP supply have voiced serious concerns about the effect that reduced access to these CSPs would have on patient care. Almost half of the hospitals (48%) indicated that an abrupt shortage of outsourced CSPs would have a "non–life-threatening but great impact" on delivery of care in their institutions; an additional 11% believed that such a shortage would lead to a "life-threatening, major disruption at the hospital."6

Table 2 presents an overview of reasons that hospitals decide to outsource their compounding needs, as well as attributes they look for in an outside vendor.6 Figure 4 shows the most commonly outsourced CSPs according to a national survey by the ASHP.28

Resources for Evaluating Potential Vendors

The ASHP offers an extensive online resource center focused on sterile compounding. One of the most important tools included in this resource center for a hospital or health system that outsources any of its sterile compounding—or is considering doing so—is the ASHP Guidelines on Outsourcing Sterile Compounding Services (http://www.ashp.org/DocLibrary/Bestpractices/MgmtGdlOutsourcing-SterileComp.aspx). There are a number of key questions that any hospital or health system that outsources CSPs should ask.29

Regulatory

- Does the vendor meet minimum requirements, such as an up-to-date pharmacy license in the state where its compounding center resides?
- Is the compounding provider licensed to ship to my state?
- If non–patient-specific preparations comprise more than 5% of

<table>
<thead>
<tr>
<th>Survey</th>
<th>Spatial Limitations, %</th>
<th>Cost, %</th>
<th>Training/Staff Competency, %</th>
<th>Time, %</th>
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</thead>
<tbody>
<tr>
<td>Douglas et al (N=412)</td>
<td>20</td>
<td>23</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Wright et al² (N=236)</td>
<td>49.1</td>
<td>47.4</td>
<td>26.8</td>
<td>39.3</td>
</tr>
</tbody>
</table>

² Respondents were given 3 choices and chose how challenging each measure was; data is listed for percentage of respondents that chose “major challenge.”

Based on references 6 and 22.
volume, is the outsourcer registered as a drug manufacturer with the FDA and Drug Enforcement Administration?

- Does the outsourcer encourage and cooperate with site visits and reviews of its licenses and certifications by all regulatory agencies, governing bodies, and customers?

**Patient Safety and Quality**

- How does the outsourcer document issues of staff competency, such as knowledge of aseptic technique, proper garbing, and hand hygiene?
- How frequently is retraining and requalification required for staff members?
- Are the results of staff training and competency assessments as well as product quality testing available for customer review?
  A good compounding pharmacy is willing to share the original results, not an edited report.
- What is the outsourcer’s philosophy for mixing nonsterile-to-sterile products?
- Where does the outsourcer obtain its ingredients, and how is the outsourcer testing the sterility of incoming products?
- Does the outsourcer’s product log contain information about the manufacturing site, where and when it was tested, and other information that allows for traceability and reliability?
- Is the outsourcer willing and able to show certification records

**Table 2. Motivation To Outsource CSPs and Vendor Selection Criteria**

<table>
<thead>
<tr>
<th>Reasons To Outsource</th>
<th>Hospitals Rating It “Very Important,” %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stability of CSPs</td>
<td>68.6</td>
</tr>
<tr>
<td>Drug shortages</td>
<td>68.1</td>
</tr>
<tr>
<td>Need a ready-to-administer form</td>
<td>67</td>
</tr>
<tr>
<td>Need extended BUDs</td>
<td>61.8</td>
</tr>
<tr>
<td>Stability/sterility testing requirements</td>
<td>61.4</td>
</tr>
<tr>
<td>Inability to compound adequate amount</td>
<td>53.7</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Vendor Selection Criteria</th>
<th>Hospitals Rating It “Very Important,” %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product quality</td>
<td>88.6</td>
</tr>
<tr>
<td>Experience and expertise</td>
<td>87.3</td>
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<tr>
<td>Reputation</td>
<td>83.8</td>
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<tr>
<td>Accreditation</td>
<td>79</td>
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<tr>
<td>Inspection history with state board of pharmacy</td>
<td>77.5</td>
</tr>
<tr>
<td>Product availability</td>
<td>75.5</td>
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<tr>
<td>Ability to provide extended BUDs</td>
<td>71.1</td>
</tr>
</tbody>
</table>

*BUD, beyond-use date; CSP, compounded sterile preparation

Based on reference 6.
for its equipment, including clean rooms, laminar flow hoods, and other automation devices?

- Have any safety problems been documented, with detailed records of the ensuing root-cause investigation? Has this information been shared with customers? Responsible compounders should be proactive and provide transparency.

- Can the compounder provide current, valid certificates of analysis on products? These should show where the product was manufactured, where it was tested, and where shipped to the company—allowing customers to follow the product’s pedigree train all the way to their own acquisition of the product.

ASHP also offers the Outsourcing Sterile Products Preparation: Contractor Assessment Tool, a comprehensive questionnaire that can be used to develop a request for proposals for these services. It contains 3 sections:

- Minimum requirements: Vendors that do not meet the minimum requirements are disqualified from consideration as an outsourcing provider of sterile products services. Those that qualify move on for additional assessments.

- Vendor assessment: This is a 4-part, 65-question survey that can be used to review and rate multiple vendors that meet the minimum requirements for a sterile compounding pharmacy. The different parts of the survey focus on registration and licensure, quality and patient safety measures, medication administration safety features, and service excellence.

- Assessment summary: This scoring section weights answers to questions on the 4 different parts of the survey: quality and safety measures are given 50% of the total value; regulatory and medication administration safety questions each get 20%; and service excellence accounts for 10% of the score. The tool recommends that only vendors who score at least 80% be considered for outsourcing sterile preparations.

When used in conjunction with an on-site assessment and USP Chapter <797> gap analysis tool, such as that provided by

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**Figure 4. Services commonly outsourced by hospital pharmacies.**

PCA, patient-controlled analgesia; TPN, total parenteral nutrition

Based on reference 28.
Critical Point for the USP <797> Compliance Study, the ASHP questionnaire provides a wealth of information to aid hospital pharmacy leaders in the decision-making process for qualifying and selecting a compounding vendor.

The Future of Pharmaceutical Compounding

After multiple smaller violations from irresponsible compounders, the NECC case has proven to be the tipping point that spurred the FDA and Congress into action. In her April 2013 testimony before the House Energy and Commerce Subcommittee on Oversight and Investigations, FDA Commissioner Hamburg recommended that Congress continue to recognize the appropriate role of states in regulating traditional compounding, while at the same time “authorizing clear and appropriate federal standards and oversight needed for non-traditional compounders that produce riskier products.”

The Senate Committee on Health, Education, Labor and Pensions (HELP), with considerable input from the FDA and other stakeholders, has created legislation that would draw clear boundaries between traditional pharmacy compounding and a newly defined entity, compounding manufacturers. The Pharmaceutical Compounding Quality and Accountability Act (S. 959) was introduced on May 15, 2013, with bipartisan co-sponsorship, and was unanimously voted out of the HELP Committee on May 22. The legislation defines compounding manufacturers as entities that compound sterile drugs without or in advance of a prescription and sell those products across state lines. Any entity other than a hospital or health system that pools sterile products, or that repackages sterile, preservative-free vials is also defined as a compounding manufacturer by the legislation. It was amended on June 19, 2013, to include provisions that enable drugs to be tracked and traced throughout the distribution system.

If this bill is enacted, the FDA will oversee compounding manufacturers’ operations. All compounding manufacturers will be required to only make products under the oversight of a pharmacist and in compliance with applicable Good Manufacturing Practices (GMPs), and they must investigate and report serious adverse events. In order to establish clear delineation between manufacturers and pharmacies, compounding manufacturers will not be allowed to register as pharmacies in state.

The legislation also preserves states’ primary role in regulating pharmacies that perform traditional compounding; a hospital pharmacy within an integrated health care network or integrated delivery system would not be required to register as a compounding manufacturer. The legislation also would give the FDA authority to designate drugs that may not be compounded by any entity because of impediments to their safe compounding. FDA-approved drugs that are available on the market may not be compounded; there is an exception to this rule in the case of medications that are on the FDA drug shortage list. Prior notice must be given to the FDA.

There are some questions that remain to be resolved within the parameters of the proposed legislation. The definition of “traditional compounding” pharmacies could be somewhat variable depending on the state. In many cases, anticipatory compounding is permitted under state law on a very small scale in advance of receiving a prescription to enhance efficiency. For example, if a compounding pharmacy knows that Dr. Smith typically sends 20 patients a week for a particular CSP, it may prepare a certain amount in anticipation of the needs of Dr. Smith’s patients. Similarly, the high-volume hospital environment often necessitates having an anticipatory inventory of certain CSPs based on historical use.

Currently, the proposed legislation does not distinguish between that form of anticipatory compounding and larger-scale manufacturing. Any entity that compounds a sterile preparation either without or in advance of a prescription will be considered a compounding manufacturer if it sells products across state lines.

The legislation has been praised by the ASHP, and welcomed by many high-volume compounders as an approach that will provide clear-cut legitimacy to those who are already adhering to appropriate guidelines, differentiating them from more slipshod operations that do not invest the necessary resources in quarantining, quality assurance, training, and product testing. Registration and inspection by the FDA, rather than by state boards of pharmacy, and adherence to applicable GMPs represent the highest assurance of quality for CSPs.

The NABP has indicated that it is supportive of rules that allow continued monitoring by state boards of pharmacy and the FDA in a comprehensive inspection process of pharmacies and compounders as well as wholesale distributors. The NABP is collecting a log of all pharmacists—involved in compounding or not—and this will be continuously updated. This reporting is expected to be a requirement in the future.

Conclusion

The old era of pharmaceutical compounding is drawing to a close, a development that responsible compounders welcome. High patient volume, limited space and resources, and noncompliance with USP Chapter <797> all place hospitals, health systems, and patients in an untenable situation. Since fall 2012, a series of FDA inspections found safety and sterility violations at 43 of the 55 compounding pharmacies it inspected. Issues included quality and sterility concerns as well as inappropriate air filtration. Hospitals that have outsourced their pharmaceutical compounding over the past decades would experience difficulties in transitioning to in-house services, as many lack the financial resources, and financial resources necessary to meet the requirements of the FDA, state boards of pharmacy, and other accrediting bodies. Yet the litany of headlines about safety violations by irresponsible compounders may inaccurately paint all sterile compounding vendors with the same broad stroke.

A combination of clear lines of federal and state oversight, a data-driven approach toward selecting CSP vendors by hospitals and health systems, and ongoing and effective monitoring of outside vendors is essential to rectify this situation. Stakeholders must voice these concerns to Congress by demanding strict, consistent processes to enact positive change and improve patient safety. Hospital pharmacy leaders may outsource the responsibility for physically preparing CSPs, but they cannot outsource the responsibility for assuring that their outsourcing pharmacy provides safe, accurately prepared CSPs so patients are not subjected to poor outcomes or iatrogenic harm.
References


Disclosures: Mr. Anderson has received honoraria from the American Society of Health-System Pharmacists. Mr. Churchill reported that he served as a consultant for Sea Medical Systems and has received honoraria from the American Society of Health-System Pharmacists. Mr. Van Hassel reported that he served on the speakers’ bureaus for Cubist Pharmaceuticals and Optimer Pharmaceuticals.

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