

## COMPOUNDING FAQ

Compounded sterile products:

# To Insource or Outsource? That Is the Question!

## Jerry Siegel, PharmD, FASHP

Clinical Associate Professor  
The Ohio State University  
Columbus, Ohio  
Managing Partner  
Safe Medication Management Associates, Inc.

## Howard Cohen, MS, RPh, FASHP

President  
Safe Medication Management Associates, Inc.

## Julie Kennerly, PharmD

PGY2 and MS Candidate  
The Wexner Medical Center  
The Ohio State University  
Columbus, Ohio

Compounded sterile products (CSP) can be prepared within the health-system pharmacy (insourced) or prepared by an external compounding pharmacy for the health system (outsourced). Since the events of this past fall related to tainted compounded products given to patients, many health care systems are considering bringing the preparation of CSPs in-house. We answer some questions about what that process entails, offering tips to help facilities determine whether a switch to insourcing makes sense.

### Q: Why outsource?

**A:** Health systems have been using compounding pharmacies to provide routinely compounded products, make better use of the labor force, and decrease the need to expand facilities. Drug shortages also have been a major driver for outsourcing certain products. Lack of available capital dollars to purchase and maintain equipment for complicated products such as total parenteral nutrition (TPN) may be another reason that pharmacy directors looked to outsource (Table 1).

### Q: What is beyond-use dating (BUD) and how does it differ in a compounding pharmacy?

**A:** United States Pharmacopeia (USP) Chapter <797> regulations define the time after a CSP is prepared via the combination of 2 or more single-use sterile products during which it can still be used.<sup>1</sup> A single-dose vial may be opened inside an ISO 5 environment and used for up to 6 hours. If it is opened outside an ISO 5 environment, it must be used within 1 hour. Unless scientific data exists to extend the dating of a CSP, it is considered to be safe from a sterility standpoint for up to 24 hours. Outsourced compounding pharmacies have their own “in-house” data to extend this standard that is considered BUD. The rigor and validity of this testing should be verified by an FDA-registered laboratory. It is presumed that the site of com-

**Table 1. Pros and Cons of Insourcing And Outsourcing CSPs**

Insourcing	
Pros	Cons
<ul style="list-style-type: none"> <li>• May improve wholesale discount by increasing volume purchased</li> <li>• Allows facility to maintain control of performance of pharmacy personnel and assure competency</li> <li>• Reduces waste due to improved inventory management and use</li> <li>• May lower overall cost of preparation</li> <li>• Allows direct oversight of pharmacy processes and responsibility for actions</li> </ul>	<ul style="list-style-type: none"> <li>• May not be able to obtain some drugs due to shortages</li> <li>• May not be able to get best prices for products such as TPN</li> <li>• Requires additional responsibility for recruitment, training, and testing of all personnel</li> <li>• Requires facility to establish or outsource BUD validation</li> <li>• Requires that facility is compliant and has certified and trained personnel</li> <li>• Requires appropriate management expertise to oversee pharmacy CSP production processes</li> </ul>
Outsourcing	
Pros	Cons
<ul style="list-style-type: none"> <li>• Allows facilities to obtain drugs with critical shortages</li> <li>• Reduces need for manpower at health system</li> <li>• Shifts responsibility for staffing to outsource pharmacy</li> <li>• Decreases waste with extended BUD</li> <li>• Increases perceived safety with USP &lt;797&gt; compliance</li> <li>• Outsource pharmacy provides oversight and responsibility for all aspects of production, including sterility, stability testing, delivery, and integrity of products</li> </ul>	<ul style="list-style-type: none"> <li>• Pharmacy has to buy drugs and may be off-contract and cannot track pedigree source</li> <li>• Labor charge is incorporated in service fee</li> <li>• Need to ensure the BUD is supported by scientific data</li> <li>• Need to inspect for compliance to USP Chapter &lt;797&gt; and conduct regular audits, including unannounced visits</li> <li>• Health facility still has to assume responsibility for pharmacy process without on-site management</li> </ul>

BUD, beyond-use dating; CSPs, compounded sterile products; TPN, total parenteral nutrition; USP <797>, United States Pharmacopeia (USP) Chapter <797> regulations

**Table 2. Differences Between Traditional Compounders and Compounding Manufacturers**

	Traditional Compounders	Compounding Manufacturers
Regulatory body	State board of pharmacy	FDA
Standard	USP Chapter <797>	Good Manufacturing Practices
Prescription requirement	Patient-specific (before or after compounding)	None
Reporting requirement	None	List of drugs compounded during the previous 6-month period to FDA
Registration fees	None	\$15,000 if >25 employees, plus cost of inspection

pounding is fully compliant with USP <797> to label the drug with the BUD.

BUD has the potential to minimize drug waste by allowing a more efficient distribution system. However, BUD also

can lead to much greater waste if the distribution of product exceeds use. Additionally, the risk factors for sterility increase over time because microorganisms such as fungi may take in excess of

5 days to reproduce in a clinically significant infectious burden. Thus, use within 24 hours may reduce the risk for causing nosocomial infections via the infusion of potentially contaminated products.

Eric S. Kastango, MBA, RPh, FASHP, the president and CEO of Clinical IQ, LLC, and his colleagues have studied compliance with USP Chapter <797> standards in health-system pharmacies and found average compliance to be approximately 75%.<sup>2</sup> Although some areas of noncompliance were specific to certain facilities, the lack of appropriate sterility testing, action plans, and employee testing were among the most frequent issues they found.

The primary distinction between manufacturers and compounders is who regulates them. Manufacturers are under the purview of the FDA, whereas individual state boards of pharmacy regulate compounding pharmacies (Table 2). The latter makes it more difficult to assure product integrity when crossing state lines, and board inspections are not nearly as rigorous as the FDA's Good Manufacturing Practice standards.

New legislation to amend the Federal Food, Drug, and Cosmetic Act with respect to compounding drugs has recently been proposed to more clearly define these differences.<sup>3</sup> The draft legislation defines *compounding manufacturer* as an entity that (1) makes sterile drug products without receiving or in advance of a prescription and introduces those drugs in interstate commerce; or (2) “repackage[s] a drug using sterile preservative-free single-dose vials or by pooling sterile drugs.” There is an exception for pharmacies located within a “health system” that compound and ship drugs for dispensing within that health system (which may include interstate shipment); this is considered a traditional compounder, subject to specified conditions, if the entity otherwise meets the definition of a traditional compounder. Under these proposed guidelines, a health system could compound sterile products from a centrally located site and distribute and use them throughout its own system.

### Weighing Benefits of Insourcing

A pharmacy director can go through the process outlined in the Figure (page 14) to assess whether it would derive sufficient return on investment (ROI) by insourcing its CSPs. In many cases, after including the cost of labor, supplies, and facility upgrades, the ROI will be positive and realized within 1 year. For a health system with the capacity to operate 5 days per week and produce 800 doses of

## COMPOUNDING FAQ

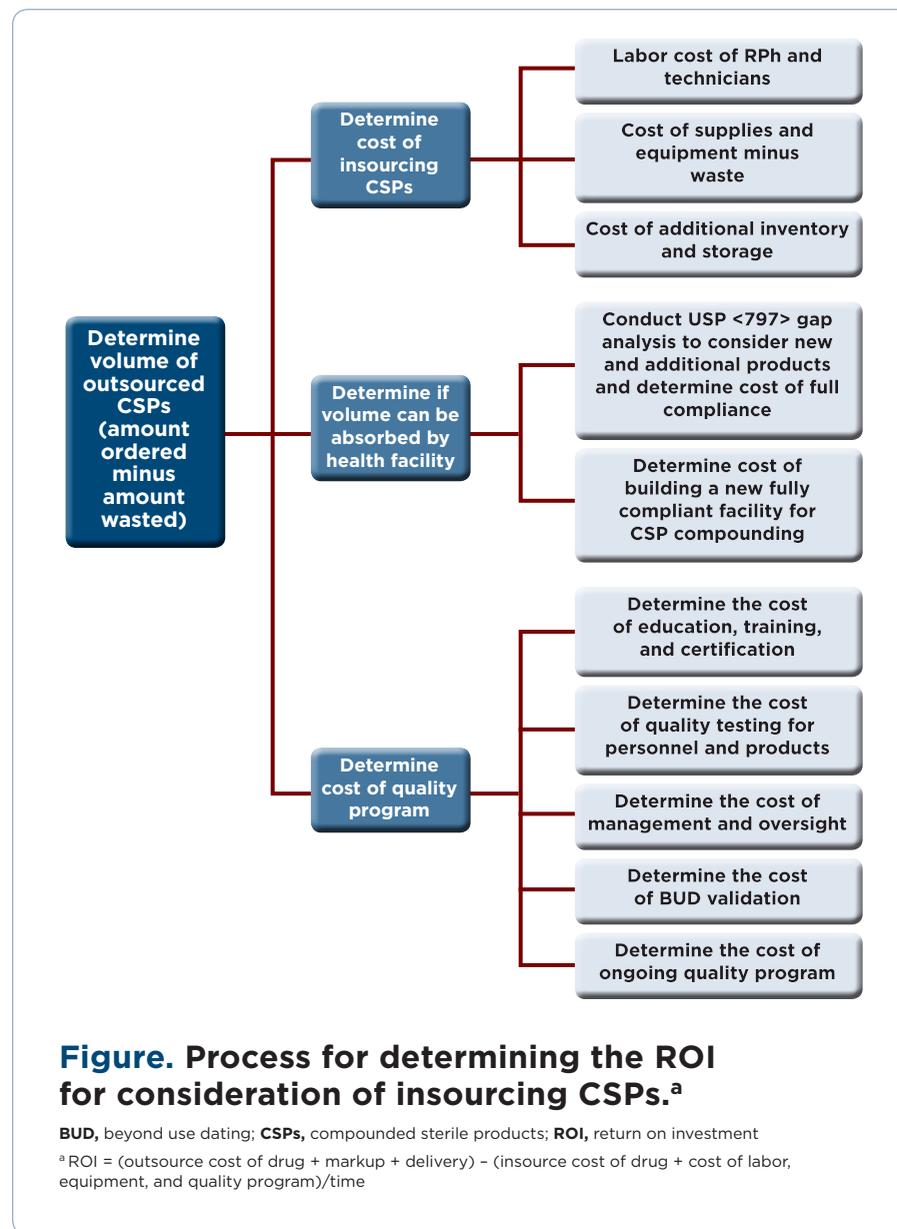
## CSPs

continued from page 10

standard CSPs per day, for example, the cost of building a new clean room could be in excess of \$1 million and labor costs could be approximately \$500,000 per year including benefits. This cost is an estimate to hire 2.4 full-time equivalent pharmacists and 4.8 technicians to work 8 hours a day on weekdays. It may take longer to realize the ROI for parenteral nutrition products because the cost to invest in compounders and tubing may offset the margin to produce the product. Each analysis should include options that provide for ROI for total outsourcing as well as outsourcing without products such as TPN, cardioplegia solutions, and elastomeric pain pumps.

When outsourcing, the director of pharmacy and the health system have the responsibility to inspect any outsourcing pharmacy, including via unannounced visits. Although a cursory tour of the facility may be impressive with respect to a clean room's appearance, the outcomes and follow-up of employee and facility sterility testing and methodology are more important.

The responsibility for full compliance with USP Chapter <797> is the same whether you outsource CSPs or insource the products. Although self-assessment may be beneficial to test compliance with USP Chapter <797> standards, it has been our experience that an unbiased expert third party will



**Figure. Process for determining the ROI for consideration of insourcing CSPs.<sup>a</sup>**

**BUD**, beyond use dating; **CSPs**, compounded sterile products; **ROI**, return on investment

<sup>a</sup>ROI = (outsourcing cost of drug + markup + delivery) - (insourcing cost of drug + cost of labor, equipment, and quality program)/time

be more stringent and not give credit for standards that are only partially met. Although a professional third party must certify all equipment such as laminar flow hoods and biological safety cabinets, the equipment in the rest of the cleanroom, such as room air-flow exchange and pressure monitoring, does require external certification. A false sense of compliance exists when a “hood certifier” places a label on a hood, although the device is not inside any sort of clean room environment.

As many directors of pharmacy evaluate the possibility of transitioning back to insourcing CSPs, they must be sure that they are, in fact, providing a safer product for their patients. There are certain things that, as a director of pharmacy and responsible pharmacist, you cannot outsource. Honesty, integrity, and responsibility are among them.

## References

1. United States Pharmacopeial Convention. General chapter <797> pharmaceutical compounding—sterile preparations. In: United States Pharmacopeia National Formulary. Rockville, MD: United States Pharmacopeial Convention; 2008.
2. Douglass K, Kastango ES, Cantor P. The 2012 USP <797> compliance survey: measuring progress. *Pharm Purch Prod*. 2012;9(10):4.
3. Pharmaceutical Compounding Quality and Accountability Act. S.959. /113th Congress. <http://thomas.loc.gov/cgi-bin/bdquery/D?d113:3:./temp/-bd9KB3:@@L&summ2=m&/home/LegislativeData.php?n=BSS;c=113>. Accessed July 16, 2013.

## 340B

continued from page 13

complexities of such issues as the new HRSA guidelines for the use of GPOs.

Apexus, HRSA's awarded prime vendor for the 340B program, has developed an educational program called 340B University, which is led by faculty from HRSA, Apexus, and the drug and pharmacy wholesale industries. The vendor also has developed online resources for covered entities, including a self-assessment tool for audits and draft policies and procedures that can be customized to their practice sites. “We are teaching HRSA's perspective and interpretation of the rules, so it's clear to all stakeholders how you should run a compliant 340B program,” said Christopher Hatwig, RPh, FASHP, the president of Apexus, in an interview. “The purpose of the audits is not to be punitive or to attack customers; it's actually to drive compliance,” said Mr. Hatwig, adding, “Every customer in the country can run a compliant program.”

—Susan Birk

## HEPARIN

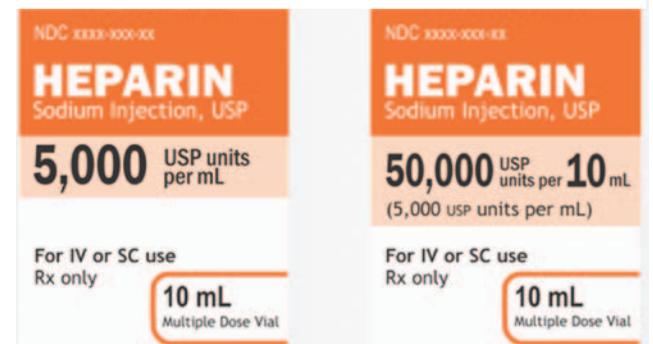
continued from page 8

the older label,” Ms. Benjamin said, “it's probably safer to remove and replace it with the new labeled product.” If the decision is made to use up the old product, the alert recommends storing it separately from the new, and using up all of the old product before dispensing the newer versions.

“It's important to walk around the organization and look at what is in stock,” Matthew Grissinger, RPh, FASCP, the director of error reporting programs at ISMP, said in an interview. “Don't think that heparin is only in the pharmacy. The pharmacist should take into account all the locations where heparin is used, in and out of the pharmacy. The emergency room, the ICU, etc, have it.”

Mr. Grissinger added, “Don't expect or hope that people will see the new label; that's not a good strategy to prevent errors. Be proactive in informing them.” He also stressed the importance of making changes to databases. “With computerized prescription order entry and bar-coding systems, make sure it matches what's on hand.”

The NAN alert also advises keeping vial sizes of all high-alert drugs, including heparin, as small as possible to reduce the chance of overdoses. “Heparin is a high-alert drug,” Ms. Benjamin said. “Special precautions are



Old (left) and new versions of heparin injection label. Both vials hold the same exact amount of medication.

Source: NAN Alert, June 10, 2013.

still needed for the new product—for example, an independent check, having someone else verify the correct dose. If possible, heparin doses should be prepared in the pharmacy.”

—George Ochoa

Ms. Benjamin and Mr. Grissinger reported no relevant financial conflicts of interest.