COMPOUNDING PROBLEMS

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In the fall of 2011 more than 20 people were injured when compounding pharmacies repackaged the anti-cancer drug, Avastin, into smaller doses for treating macular degeneration. Many lost their eyesight and one patient suffered brain damage from the resulting infections.

Since then numerous other infections from a variety of compounded drugs have occurred.[1] For example, one year later approximately 800 patients were affected by fungal-contaminated steroid injections prepared by the New England Compounding Pharmacy.[2] More than 750 were seriously injured with more than 60 patients dying as a result of spinal meningitis and other infections from these injections. Most recently, the loss of visual acuity by several patients after routine cataract surgery at a prominent Dallas-based surgery center has been attributed to a compounded steroid antibiotic solution prepared by a 503A compounding pharmacy.[3] An FDA investigation into this incident is ongoing.

This article addresses manufacturing and multi-vial use issues with respect to use of compounded sterile preparations (CSPs) in the ASC, including recommendations for standardizing drug protocols so as to reduce liability exposure.

CLASSES OF MANUFACTURING

Over the years compounding pharmacies, which traditionally had dealt with providing compounded drugs to individual patients, have moved into the manufacture of batch quantities of drugs. The FDA had no legal basis for oversight of compounding pharmacies, unlike their oversight of commercial drug manufacturers, which were required to submit approval applications and have regular FDA inspections of their facilities to ensure compliance to "Good Manufacturing Procedures (GMPs)." (GMPs are those regulations designed to ensure that the manufactured drugs are safe and efficacious, and that they meet purity and potency standards.)

In November 2013 Congress passed the Drug Quality and Security Act (DQSA)[4] to give the FDA authority to regulate compounding pharmacies. The DQSA created two classes of manufactured compounded drugs. Section 503A pertains to drugs created in traditional compounding pharmacies and Section 503B pertains to drugs created in what are now called Outsourcing Facilities.

Table 1 compares 503A and 503B requirements.

WHAT PRESCRIBERS NEED TO KNOW

The major difference between traditional compounding pharmacies (503A) and the newly created outsourcing facilities (503B) is that compounding pharmacies only have the authority to compound drugs for individually identified patients (doctor's prescription), whereas the outsourcing facilities could engage in batch manufacturing but were required to be in compliance with all GMP regulations for the manufacture of drug products (21CFR210 and 21CFR 211) and accessible for FDA inspection.

Because 503B Outsourcing Facilities must meet GMP standards for manufacturing compounded sterile preparations (CSPs), they are legally permitted to manufacture a CSP in bulk rather than prepare a CSP for a specific patient. The FDA maintains a web page of 503b Outsourcing Facilities. **Table 2** summarizes the status of 503B applicants as of the end of June 2017.[5]

Note that to date most, if not all, compounding pharmacies that have attempted to upgrade to an outsourcing facility status have failed their initial FDA GMP inspections for serious deficiencies in sterile manufacturing

TABLE 1. COMPARING DRUG QUALITY AND SECURITY ACT (DQSA) REQUIREMENTS FOR COMPOUNDING PHARMACIES VS. OUTSOURCING FACILITIES

	503A COMPOUNDING PHARMACIES	503B OUTSOURCING FACILITIES
Regulatory authority	State Boards of Pharmacy FDA Registration and Inspection	FDA Registration and Inspection States may add requirements
Applicable standards	USP, FDA 503A Policy Guide	FDA GMP (21CFR210 & 211) plus additional state requirements
FDA inspection	Under authority to enforce 503A	FDA authority to enforce GMP regulations
Licensing	State Boards of Pharmacy	FDA
Inspection	FDA State Boards of Pharmacy	If additional state requirements
Limitations on services	Individual prescription only Limited anticipatory compounding	Batch processing May maintain inventory

TABLE 2. STATUS OF 503B APPLICANTS, JUNE 2017-SUMMARY OF DATA FROM FDA WEBSITE BELOW[5]

Facilities registered with the FDA as 503B Facilities	71	
After inspection, received an FDA Warning Letter, Notice for a Regulatory Meeting, or other letter, and subsequently ceased sterile operations and/or recalled sterile products	26	36.62%
Inspected by FDA, issues found but final outcome to be determined Unaudited Inspected with no serious issues	32 13 0	45.07% 18.31% 0%

process and controls, and are looking at substantial upgrades to facilities and procedures to be compliant.

MULTI-USE VIALS

The Centers for Disease Control (CDC) issued a position statement in 2011 limiting the use of multi-dose vials to a single patient. CDC defined a multi-dose vial as a vial of liquid medication intended for parenteral administration (injection or infusion) that contains more than one dose of medication. Eye drops do not meet this definition, yet we continue to see instances of surveyors erroneously citing ASCs for inappropriate (i.e., multiple-patient) use of multi-dose eye drops. Therefore it is important to understand the definition of a multi-dose vial and have established policies and procedures for administration of multi-dose eye drops.

Focus on eye drop administration coupled with zeal for improved efficiency and cost management has driven ophthalmic ASCs toward adoption of a dilating compound solution for pre-op dilation. Before 2009, ASCs mixed their own dilating solutions. Since then, we have gotten an education on drug compounding. Following specific United States Pharmacopeia (USP) guidelines and infection control standards, only immediate-use drug compounding is allowed in a surgery center.

The investment in infrastructure and training required to meet compounding standards, however, are generally cost prohibitive. This led ASCs to outsource CSPs. Continuing reports of patient complications, questions, and concerns related to drug compounding remain, in part due to evolving regulations at the state and federal level.

RECOMMENDATIONS

On a practical level it makes sense to standardize your drug protocols as much as possible. Adoption of a single dilating protocol can dramatically improve efficiency and minimize medication errors. In the absence of a cost-effective unit dose preparation, outsourcing a dilating solution makes sense.

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> It is risky to assume your vendor produces CSPs to regulatory standards.

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However, it is risky to assume your vendor produces CSPs to regulatory standards. Current regulatory scrutiny and widely available information on issues such as risk of infection, inaccurate dosages, and drug mix-ups, puts prescribers on notice. ASCs must be familiar with the new regulations and have procedures in place to assure that the drugs they prescribe are produced to current regulatory standards. Not doing so exposes their patients to unnecessary risk and themselves to potential liability.

To reduce liability exposure the ASC should conduct due diligence on the manufacturing facility, which includes at a minimum:

- Required state and federal licenses and registration
- Safety records
- FDA inspection records, warning letters and other documentation[6] as a 503B facility to assure there are no issues with processes affecting desired compounds
- Staff training records
- Policies and procedures for stability and sterility

For a more comprehensive list, see ASHP Guidelines on Outsourcing Sterile Compounding Services.[7] **AE**

NOTES

[1]Eisler, P. (2012, Oct. 11). Deaths, infections tied to "compounding" drugs. *USA Today.* Retrieved from https://www.usatoday.com/story/news/nation/2012/10/11/compounding-pharmacies-deaths/1626753/

[2]----------. (2017, Sept. 10). Compounding center meningitis outbreak. Wikipedia. Retrieved from https://en.wikipedia.org/wiki/New_England_Compounding_Center_meningitis_outbreak

[3]Staff. (2017, June 9). Drugs from Dallas compounder linked to vision loss. Review of ophthalmology. Retrieved from https://www.reviewofophthalmology.com/article/drugs-from-dallas-compounder-linked-to-vision-loss

[4]--------. (2017, Sept. 9). Drug quality and security act. Wikipedia. Retrieved from https://en.wikipedia.org/wiki/Drug_Quality_and_Security_Act

[5]FDA. (2017, Aug. 9). Registered outsourcing facilities. U.S. Food and Drug Administration. Retrieved from https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm378645.htm

[6]Federal Food, Drug and Cosmetic Act. Warning Letters are only issued for violations that may actually lead to an enforcement action (product seizures, injunctions, arrests, and convictions) if the documented violations are not promptly and adequately corrected. In the case of 503B applicants the FDA is issuing other letters of violation and notices for a regulatory meeting with the FDA.

[7]American Society of Health-System Pharmacists. (2015). ASHP guidelines on outsourcing sterile compounding services. Retrieved from https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines-outsourcing-sterile-compounding-services.ashx?la=en



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