U.S. Department of Health and Human Services

Office of Inspector General

Most Hospitals Obtain Compounded Drugs From Outsourcing Facilities, Which Must Meet FDA Quality Standards

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Suzanne Murrin
Deputy Inspector General
for Evaluation and Inspections

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What OIG Found

Most hospitals that obtained non-patient-specific compounded drugs from outside compounders obtained them from what the Food and Drug Admnistration (FDA) calls outsourcing facilities—compounders that are registered with FDA. In fact, 89 percent of hospitals that obtained non-patient-specific compounded drugs did so exclusively from outsourcing facilities, 9 percent of such hospitals obtained at least some from outsourcing facilities, and just 2 percent obtained them exclusively from unregistered compounders. We provided FDA with a list of compounders sorted by registration status, which it can use to prioritize followup.

Key Takeaway
Most hospitals obtain non-patient-specific compounded drugs from outsourcing facilities—facilities that are registered with FDA. Factors associated with quality, including registration with FDA as an outsourcing facility, are among the most important factors that hospitals consider when they decide where to obtain their non-patient-specific compounded drugs.

Hospitals reported that quality considerations—including FDA registration; State and Federal enforcement actions; product recalls; and quality assurance documentation—drive their decisions on where to obtain non-patient-specific compounded drugs. Hospitals rated quality considerations as extremely important when choosing compounders. One expert told us, "… I would be very hesitant to purchase from a nonregistered facility."

Of hospitals that compounded non-patient-specific drugs in their own pharmacies, only 2 percent had considered registering those pharmacies with FDA as outsourcing facilities, and only one hospital had actually registered its compounding facility. Cost, as well as equipment and facility design limitations, were extremely important factors for hospitals in deciding whether to register their pharmacies as outsourcing facilities.

What OIG Recommends and How the Agency Responded

OIG recommends that FDA further communicate with hospitals about the importance of obtaining their non-patient-specific compounded drugs from outsourcing facilities. We also recommend that FDA take appropriate followup actions with the unregistered compounding facilities on the list that we provided; these facilities may not be in compliance with Federal law. FDA's followup could include for-cause inspections and any advisory or enforcement actions that are warranted. FDA concurred with our recommendations.

Why OIG Did This Review

To provide FDA with insights to improve its oversight of compounders and enhance patient safety, OIG determined the extent to which hospitals purchase non-patient-specific compounded drugs from outsourcing facilities. Only compounders registered with FDA as outsourcing facilities can legally compound and distribute non-patient-specific drugs.

In response to deaths from an outbreak of fungal meningitis caused by contaminated compounded injections, Congress passed the Drug Quality and Security Act in November 2013. This legislation enhanced FDA's authority over facilities that perform large-scale compounding of non-patient-specific drugs. It distinguished the work of these facilities from traditional pharmaceutical compounding, which is done on a patient-specific basis. The Drug Quality and Security Act allows compounders that are registered as outsourcing facilities with FDA to compound and distribute drugs without a patient-specific prescription. FDA must inspect such facilities according to a risk-based schedule.

How OIG Did This Review

We selected a stratified random sample of 601 Medicare-participating hospitals and sent them a questionnaire, achieving an overall 94-percent response rate. We asked the hospitals detailed questions about where they obtain non-patient-specific compounded drugs and the factors they considered in choosing where to obtain them. To determine the registration status of the compounding facilities that the hospitals identified, we compared those facilities' names to FDA's list of registered outsourcing facilities as of January 2018.

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BACKGROUND

Objectives

To determine the extent to which Medicare-participating hospitals:

1. acquire compounded drugs from entities registered as outsourcing facilities with the Food and Drug Administration (FDA), and
2. consider registering their pharmacies with FDA as outsourcing facilities.

In 2012, contaminated steroid injections compounded by the New England Compounding Center caused a nationwide meningitis outbreak resulting in 64 deaths and a total of 753 cases of fungal infection.[1] The outbreak raised concerns about oversight of compounded drugs and prompted Congress to pass the Drug Quality and Security Act (DQSA) in November of 2013.[2]

The DQSA added a new section 503B to the Federal Food, Drug, and Cosmetic Act (FD&C Act) and established requirements for compounding facilities that elect to register with FDA. FDA calls such registered facilities outsourcing facilities.[3] Only entities that register and comply with section 503B of the FD&C Act can compound and distribute drugs without a patient-specific prescription.

Outsourcing facilities are subject to FDA inspections in accordance with a risk-based schedule.[4] FDA inspections assess the facilities for compliance with the FD&C Act, including section 503B and the current good manufacturing practice (CGMP) requirements under section 501(a)(2)(B). These inspections frequently identify CGMP violations. One such violation would be poor aseptic technique that may result in a lack of sterility that facilities must address to protect the public's health.[5] FDA lists outsourcing facilities and their inspection results on its website, thereby promoting transparency and compliance with quality standards.[6] In addition, outsourcing facilities must indicate to FDA each year whether they intend to compound drugs that are in shortage.[7]

Use of compounded drugs is widespread in hospitals. Prior Office of Inspector General work found that 92 percent of Medicare-participating hospitals used compounded sterile drugs in 2012, and that 79 percent of those hospitals contracted with at least one compounding facility to produce these products.[8] In a 2014 letter to hospitals, FDA encouraged them to purchase their compounded drugs from outsourcing facilities because such facilities have greater assurances of quality (see Exhibit 1).[9] Our current report determines the extent to which hospitals have purchased their compounded drugs from outsourcing facilities; provides FDA with

further data on the landscape of compounded drugs; and adds to OIG's body of work on this important topic.

Exhibit 1. Excerpt from FDA's 2014 Letter to Hospitals

> *As a purchaser of compounded drugs, you can play an important role in improving the quality of compounded drugs by requiring compounding pharmacies that supply drugs to your facility to register as outsourcing facilities. Once they register, you and the patients you serve can be assured that FDA will inspect these facilities on a risk-based schedule, hold them to CGMP requirements, monitor adverse events reports they are required to submit to the agency, and require appropriate labeling.*

Pharmaceutical Compounding

Compounding is generally the practice of combining, mixing, or altering a prescription drug to meet the needs of an individual patient. For example, a licensed pharmacist may compound a drug without a certain dye to which a patient may be allergic, or the pharmacist might create a liquid form of a drug for a patient who is unable to swallow a pill. Traditionally, licensed pharmacists and physicians compound a drug for an individual patient and dispense it upon the receipt of a prescription. In contrast, outsourcing facilities can engage in large-scale compounding of non-patient-specific (NPS) drugs—a process akin to conventional manufacturing.[10]

Unlike with most prescription drugs, FDA does not review and approve compounded drugs. Therefore, FDA does not verify their safety, effectiveness, or quality prior to their being marketed in the United States. Hospitals may contract with multiple outside compounders in addition to compounding drugs within their own pharmacies.

The Drug Quality and Security Act

The DQSA added a new section 503B to the FD&C Act, thereby enhancing FDA's oversight authority over facilities that perform large-scale non-patient-specific compounding of drugs.[11] State boards of pharmacy have primary responsibility for overseeing traditional compounding pharmacies, which perform patient-specific compounding (i.e., they prepare drugs for identified individual patients), distribute those products pursuant to patient-specific prescriptions, and otherwise comply with section 503A of the FD&C Act.

Section 503B of the FD&C Act created a new category of compounding facilities—called outsourcing facilities—that often compound and distribute drugs without a patient-specific prescription. Unlike with traditional pharmacy compounding, outsourcing facilities may legally compound and distribute drugs without a patient-specific prescription if they register with FDA and comply with section 503B of the FD&C Act.

Section 503B of the FD&C Act does not limit the quantities of compounded drugs that outsourcing facilities may sell without a patient-specific prescription anywhere in the United States. If an outsourcing facility complies with section 503B of the FD&C Act, it is eligble for exemption from certain FD&C Act requirements, including from the drug-approval process required for conventional manufacturers. See Exhibit 2.

Exhibit 2. Outsourcing facilities and outside compounders, explained

Outsourcing facility

A compounder that is registered with FDA as a 503B outsourcing facility. Registration with FDA enables a facility to compound and distribute drugs without a patient-specific prescription (referred to as NPS drugs throughout this report), provided that the facility meets certain statutory conditions. Outsourcing facilities are subject to routine FDA oversight.

Outside compounder

Any entity other than a hospital's pharmacy that produces compounded drugs. An outside compounder may be an outsourcing facility or an unregistered facility.

Among other things, under section 503B of the FD&C Act, outsourcing facilities must meet the stringent quality standards found in FDA's CGMP requirements under section 501(a)(2)(B) of the FD&C Act and parts 210 and 211 of Title 21 of the Code of Federal Regulations.[12] FDA's CGMP requirements establish baseline standards for the physical plant, equipment, and production controls in place at registered outsourcing facilities.[13]

FDA's goal is generally to inspect an outsourcing facility within 2 months of the facility's initial registration.[14] As of September 21, 2018, 73 compounding facilities had registered as outsourcing facilities with FDA.[15] As of January 2017, FDA had conducted 85 inspections of outsourcing facilities—it had inspected all facilities at least once, and had inspected some facilities more than once. Almost all of these inspections resulted in FDA's issuing an FDA Form 483 to notify the facilities of objectionable conditions.[16] FDA encourages facilities to respond to the form in writing with corrective action plans and to implement the plans expeditiously. If the objectionable conditions warrant further action, FDA may take an advisory or enforcement action, including sending the facility a warning letter or bringing an action for seizure or injunction.[17, 18]

Compounding Within a Hospital Pharmacy

Hospital pharmacies can fulfill an array of patient needs, compounding both non-patient-specific (NPS) and patient-specific drugs to varying degrees. Sometimes, hospital pharmacies may not be able to compound a patient-specific drug in an emergency situation. In such cases, hospitals sometimes compound those drugs without a patient-specific prescription. Federal law does not permit a hospital pharmacy to compound and distribute non-patient-specific drugs within or outside of the hospital. In its 2016 draft guidance on hospital compounding, FDA recognizes that hospital pharmacies may need NPS supplies of certain compounded drugs,[19] and FDA recommends that hospitals obtain NPS compounded drugs from outsourcing facilities. The draft guidance also proposes certain parameters within which FDA generally would not intend to object if hospitals compounded and distributed NPS drugs.

FDA's Proposed Risk-Based Approach to Manufacturing Standards

In January 2018, FDA released its *2018 Compounding Policy Priorities Plan*. According to the plan, FDA's priorities include transitioning from the current CGMP regulations to promulgating more specific CGMP regulations for outsourcing facilities.[20] In December 2018, FDA issued revised draft guidance outlining a risk-based approach to CGMP requirements. This approach seeks to recognize the differences between outsourcing facilities and conventional drug manufacturers while protecting patients from substandard compounded drugs.[21]

Related OIG Work

This study is part of a larger body of OIG work examining hospital use of compounded drugs. In 2013, OIG found that among Medicare hospitals that used compounded drugs, 95 percent prepared compounded sterile drugs onsite and 79 percent of these hospitals also purchased compounded sterile drugs from external compounding facilities.[22]

An OIG study published in 2014 found that Medicare claims data do not include identifying information for external compounding facilities that provide a hospital with compounded drugs. Including such identifying information on claims would help the Centers for Medicare & Medicaid Services (CMS) and hospitals identify the source(s) of future outbreaks.[23] CMS did not concur with OIG's recommendation to explore including that information, citing questions about CMS's authority to do so and the significant resources that would be necessary to adjust the claims processing system.

In 2015, OIG released a study that examined Medicare's oversight of hospitals' practices related to compounding. This study found that Medicare's oversight addresses most of the expert-recommended practices related to compounding some of the time, but the study did not generally review hospitals' contracts with external compounding facilities. These

contracts help ensure that external compounding facilities provide safe, nontainted compounded drugs to hospitals.[24] CMS implemented our recommendations for it to train surveyors on standards from nationally recognized organizations related to safe compounding practices and for it to amend its interpretive guidelines to address contracting with outside compounding pharmacies.

Methodology

Scope

This report is national in scope. We selected our sample from all Medicare-participating acute-care hospitals as of September 2017. From that population, we focused our analysis on the estimated 80 percent of hospitals that obtained NPS compounded drugs from any source (hospital pharmacy, outside compounder, and/or outsourcing facility).[25]

Data Sources and Analysis

To conduct this study, we relied on a survey of hospitals, FDA's registry of outsourcing facilities, and stakeholder interviews. Stakeholders included officials from FDA and experts in pharmaceutical compounding and hospital compounding.

We selected a sample of acute-care hospitals to determine where they obtained their patient-specific and NPS compounded drugs. To do so, we first identified 4,746 acute-care hospitals that participated in Medicare in 2017.[26] We then stratified that population by size (bed count) and by whether a hospital was known to have registered its pharmacy as a 503B outsourcing facility. We selected 300 large hospitals(≥50 beds), 300 small hospitals (<50 beds), and the 1 hospital with a pharmacy that was on FDA's registry of outsourcing facilities at the time we selected our sample, resulting in a total sample of 601 hospitals.[27] See Exhibit 3 for additional details on the sample size and response rates.

Exhibit 3. Sample and Population Data for Medicare-Participating Hospitals Surveyed for This Study

Strata Descriptions	Number of Hospitals in Population	Number of Hospitals in Sample	Response rate
Large hospitals (≥50 beds)	2925	300	93%
Small hospitals (<50 beds)	1820	300	94%
Hospital registered as outsourcing facilities	1	1	100%

We administered our electronic questionnaire between October 20, 2017, and January 4, 2018. We analyzed the responses as a whole and by hospital size. We requested information on (among other related questions) whether hospitals considered registering their pharmacies as outsourcing facilities, the hospitals' sources for their compounded drugs, and factors that hospitals considered in sourcing their compounded drugs. For purposes of this report, we considered hospitals that reported compounding NPS drugs in their pharmacies or obtaining them from outside compounders to be using NPS compounded drugs.

To determine the registration status of each source of compounded drugs, we compared by name the sources that responding hospitals identified and FDA's registry as of January 2, 2018.

Limitations

Our review relied on self-reported information from hospitals. We did not independently verify hospitals' responses.

Standards

We conducted this study in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

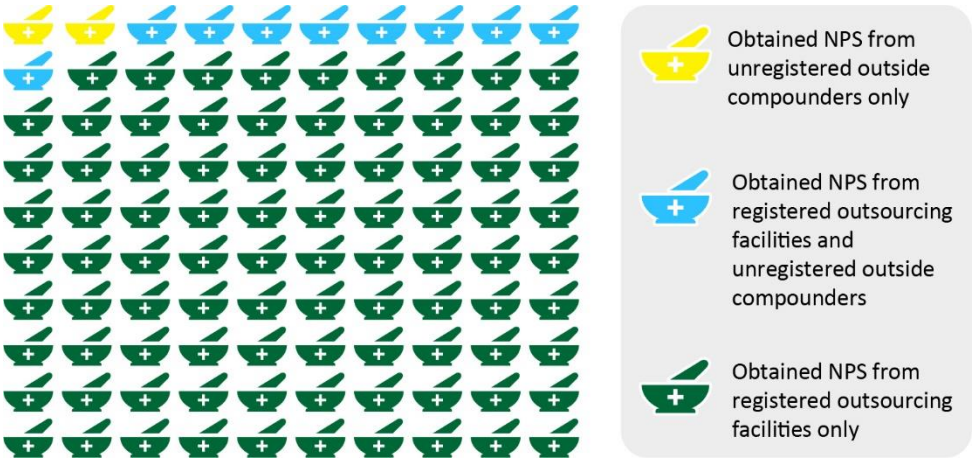
FINDINGS

Most hospitals that obtained NPS compounded drugs from outside compounders got them from outsourcing facilities

Outsourcing facilities are major sources for hospitals' compounded drugs. Among hospitals that obtained NPS compounded drugs from outside compounders, 89 percent of hospitals obtained them only from compounders that were registered with FDA as 503B outsourcing facilities. This means that the facilities are subject to FDA inspection and reporting requirements, and that they must adhere to CGMP requirements. See Appendix D for point estimates and 95-percent confidence intervals for findings pertaining to the FDA registration status of outside compounders from which hospitals obtain NPS compounded drugs.

Among hospitals that obtained NPS compounded drugs from outside compounders, about 11 percent obtained at least some of these drugs from unregistered facilities: 9 percent both from outsourcing facilities and unregistered facilities, and 2 percent exclusively from unregistered facilities (see Exhibit 4). Unregistered facilities that distribute NPS compounded drugs are not in compliance with the FD&C Act and are a potential significant threat to public health. We provided the list of all identified outside compounding facilities sorted by registration status to the FDA for appropriate followup.[28]

Exhibit 4. Most hospitals that obtained NPS compounded drugs from outside compounders got them from outsourcing facilities.

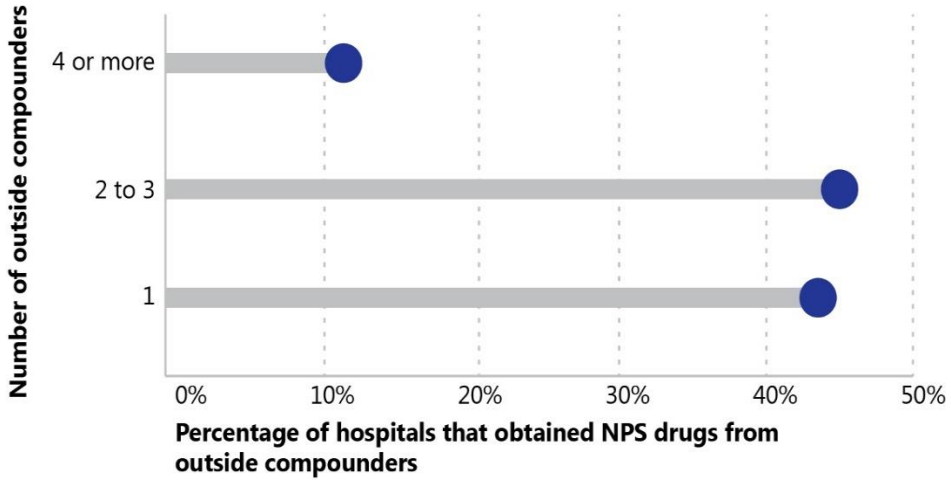


Source: OIG analysis of survey data from Medicare-participating hospitals, 2017.

Many hospitals obtain NPS compounded drugs from multiple outside compounders. Over half of hospitals that obtained such drugs from outside compounders obtained them from more than one outside compounder.

Among all of these hospitals, almost 90 percent used between one and three outside compounders (see Exhibit 5).

Exhibit 5. Most hospitals that obtained NPS compounded drugs obtained them from more than one outside compounder



Source: OIG analysis of hospital-reported data. Analysis limited to hospitals that obtained non-patient-specific compounded drugs in the 12 months prior to October 2017.

Three kinds of drugs—narcotics/controlled substances, patient-controlled analgesia, and epidurals—were among those commonly obtained from outside compounders and compounded in hospitals' own pharmacies. See Appendix A for information on the kinds of drugs that hospitals obtain from outside compounders. See Appendix B for information on the kinds of drugs that hospitals compound in their own hospital pharmacies.

Nearly half (45 percent) of hospitals faced some challenges in obtaining all the NPS compounded drugs they sought from outside compounders. Of these hospitals, 76 percent were unable to obtain a drug on FDA's drug shortage list from outside compounders.[29] Outsourcing facilities generally cannot make products that are essentially copies of approved drugs, but drugs that appear on FDA's drug shortage list at the time of compounding, distribution, and dispensing are not considered to be essentially copies of approved drugs.[30] However, some factors that contribute to drug shortages—such as lack of raw materials—affect outsourcing facilities and conventional manufacturers alike. The unpredictability of drug shortages also makes it risky for outsourcing facilities to invest in compounding a drug that remains for an indefinite period on the drug shortage list.[31]

Of the hospitals that reported facing challenges in obtaining all the NPS compounded drugs they sought from outside compounders, more than a quarter specifically reported challenges in obtaining patient-controlled

analgesia, operating room syringes, narcotics/controlled substances, and pitocin/oxytocin from outside compounders. More information on the challenges that hospitals faced in obtaining NPS compounded drugs is included in Appendix C.

Hospitals reported that quality considerations, including whether a compounder was registered as an outsourcing facility, drive decisions about where to obtain compounded drugs

Nearly all hospitals rated quality considerations as extremely important in choosing sources for compounded drugs. (See Exhibit 6 for descriptions of the factors we defined as quality considerations for the purposes of this report.) Overall, 94 percent of hospitals reported that a source's history of Federal enforcement actions, such as product seizures or injunctions, was extremely important. Likewise, 94 percent identified the history of State actions, such as suspension or revocation of a State license, as being extremely important. Furthermore, 92 percent rated product recalls, quality assurance documentation, and 503B registration status as being extremely important. In fact, one stakeholder told us that FDA registration was a way to determine whether a compounder "passed muster."

> ***"If I was a pharmacy director, I would be very hesitant to purchase from a nonregistered facility."***
> **– Pharmacy expert**

Finally, stakeholders with whom we spoke noted that the 2012 meningitis outbreak heightened hospitals' awareness of the risks associated with compounding, and that it focused their attention on quality, risk management, and liability.

Exhibit 6. Factors Defined as Quality Considerations for This Report

- History of State actions against facility (e.g., suspension or revocation of State license)
- History of Federal enforcement actions against facility (e.g., seizure or injunction)
- History of product recalls and/or cessation of sterile operations
- Quality assurance documentation
- Registration with FDA as a 503B outsourcing facility
- Facility's accreditation status
- Appropriate licensure of pharmacy staff
- Warning letters issued based on FDA inspection findings
- Facility's reputation
- Staff training and competency assessment documentation
- Observations listed on FDA Form 483

Although the cost of compounded drugs matters to many hospitals, it does not appear to drive hospital decisions about where to obtain compounded drugs as strongly as do quality considerations. For example, 58 percent of hospitals considered the cost of the compounded drugs extremely important in choosing where to obtain them. A similar proportion—53 percent—considered contracts with group purchasing organizations, which allow hospitals to leverage their buying power for discounts, to be extremely important. Less than half (49 percent) reported that their own purchasing histories with compounders were extremely important. See Appendix E for additional factors that hospitals consider when making decisions about where to obtain compounded drugs.

Hospitals rarely considered registering their pharmacies with FDA as outsourcing facilities

Fewer than 2 percent of hospitals that compound NPS drugs in their pharmacies had considered or were currently considering registering their pharmacies as 503B outsourcing facilities. Registering as 503B outsourcing facilities and complying with the FD&C Act represents a high bar for hospitals, which generally compound under less stringent conditions than those that must be met by outsourcing facilities. Stakeholders told us that meeting this bar could represent a "huge leap in cost and talent" for hospitals, calling for initial investments of $3 million to $10 million. Hospitals reported both that initial cost of making a pharmacy CGMP-compliant and the limitations of their equipment and facility design were extremely important in deciding whether to register.

Nearly half of hospitals (47 percent) obtained NPS compounded drugs from both their own pharmacies and one or more other source(s)—usually, an outsourcing facility. Hospitals rarely relied solely on their own pharmacies to provide NPS compounded drugs; just 8 percent did so. Therefore,

hospital pharmacies that compound NPS drugs may have little incentive to expend the significant amount of time and resources required to make their pharmacies CGMP-compliant. See Appendix D for compounding and purchasing practices for NPS drugs.

Just one hospital pharmacy, associated with a large hospital system, is registered with the FDA.

CONCLUSION AND RECOMMENDATIONS

FDA stated that it is committed to implementing the Drug Quality and Security Act (DQSA) in a way that enhances patient safety by protecting patients from unsafe, ineffective, and poor-quality compounded drugs while preserving access to lawfully compounded drugs.[32] The DQSA created outsourcing facilities, a new category of drug-compounding facility that is subject to FDA registration and oversight. Patient safety is advanced when hospitals choose to obtain compounded drugs from outsourcing facilities that are registered with FDA. Outsourcing facilities must adhere to current good manufacturing practices, report adverse events to FDA, and label products with certain information. According to our analysis, hospitals have largely chosen to obtain their NPS compounded drugs from such facilities. They based their decisions primarily on factors related to quality, and FDA registration was key among these factors.

In 2014, FDA wrote to hospitals about the DQSA and urged them to obtain their compounded drugs from outsourcing facilities. Most heeded that call, but 11 percent still obtain at least some of their NPS compounded drugs from unregistered compounders. We provided a list that included those unregistered facilities to FDA for its information and appropriate followup.

In light of our findings, we offer FDA the following recommendations as it continues to implement the DQSA:

FDA should further communicate to hospitals the importance of obtaining NPS compounded drugs from outsourcing facilities

Hospitals are the frontline of patient safety, and safely compounded drugs are necessary for effective patient care. To that end, FDA should further promote how hospitals can better ensure quality and patient safety by obtaining NPS compounded drugs from outsourcing facilities. FDA could communicate to hospitals by writing to them; posting information on its website; or publishing information or an article; among other options. In doing so, FDA could provide additional information on its oversight of outsourcing facilities—including information on its inspection and enforcement activities—to help hospitals make decisions about where to obtain compounded drugs. To help hospitals obtain drugs that are on FDA's drug shortage list, FDA could make available information about outsourcing facilities that have informed it of their intent to compound such drugs. Finally, we encourage FDA to evaluate opportunities for enhancing its website as a tool for hospitals that wish to assess the compliance history of outsourcing facilities.

FDA should take appropriate followup action with the unregistered compounding facilities on the list that we provided

NPS compounders that are unregistered and are not operating in compliance with section 503B of the FD&C Act could pose a public health threat. We provided a list that included unregistered NPS compounders to the FDA. FDA should review that list and take appropriate actions with unregistered compounders, such as conducting for-cause inspections and any advisory or enforcement actions warranted.

AGENCY COMMENTS AND OIG RESPONSE

FDA concurred with both of our recommendations.

In response to our first recommendation, FDA agreed that ongoing outreach to hospitals about obtaining compounded drugs from registered outsourcers is important. FDA stated that it regularly engages with hospitals and health-system stakeholders regarding drug compounding and applicable law and policy, and that its specific engagement efforts include holding annual listening sessions, developing policy on compounding in hospital and health-system settings, and continuing to post information about the products that outsourcing facilities have recently produced, which may include drugs in shortage.

In response to our second recommendation, FDA stated that it has used the list we provided to conduct inspections and has confirmed that some sites distributed NPS compounded drugs. Those inspections also identified objectionable conditions, and some have led to a recall. FDA stated that it will continue to take appropriate followup actions.

OIG appreciates FDA's concurrences and its commitment to implementing the DQSA. FDA's continued efforts in NPS compounding can help protect patients from unsafe, ineffective, and poor-quality compounded drugs while preserving access to lawfully compounded drugs.

For the full text of FDA's comments, see Appendix F.

APPENDIX A: Types of drugs obtained by hospitals from outside compounders on a non-patient-specific basis

Percentage of hospitals that obtained NPS compounded drugs with the following characteristics from outside compounding facilities

Drug	Sample Size	Point Estimate (95-Percent Confidence Intervals)	Independent Group T-Test By Hospital Size (P-Value)
High-volume compounded sterile preparations	421	57.6% (53.2%-62.0%)	Small: 32.1% Large: 67.9% (<0.0001)
Low-volume compounded sterile preparations	421	61.2% (56.7%-65.6%)	Small: 54.6% Large: 64.0% (0.0752)
High-risk compounded sterile preparations	421	24.5% (20.7%-28.7%)	Small: 15.2% Large: 28.2% (0.0047)
Products in shortage	421	58.1% (53.7%-62.4%)	Small: 30.9% Large: 69.0% (<0.0001)
Emergency cart medications	421	25.6% (21.7%-29.8%)	Small: 17.0% Large: 29.0% (0.0103)
Research/study drugs	421	0.3% (0.04%-1.8%)	Small: 0% Large: 0.4% (0.4919)

Percentage of hospitals that obtained NPS compounded drugs with the following mode of delivery or dosage form type from outside compounding facilities

Drug	Sample Size	Point Estimate (95-Percent Confidence Intervals)	Independent Group T-Test By Hospital Size (P-Value)
Operating room syringes	421	63.0% (58.6%-67.2%)	Small: 43.0% Large: 71.0% (<0.0001)
Patient-controlled analgesia	421	70.6% (66.5%-74.4%)	Small: 47.3% Large: 80.0% (<0.0001)
Epidurals	421	55.0% (50.5%-59.3%)	Small: 29.7% Large: 65.1% (<0.0001)
Critical care infusions	421	32.0% (27.8%-36.4%)	Small: 6.1% Large: 42.4% (<0.0001)
Intrathecals	421	4.7% (3.1%-7.2%)	Small: 1.8% Large: 5.9% (0.0756)
Eye drops	421	8.2% (6.1%-11.0%)	Small: 12.1% Large: 6.7% (0.0689)
Creams/ointments/suppositories or other topical agents	421	9.6% (7.2%-12.7%)	Small: 9.1% Large: 9.8% (0.8237)
Tablets/capsules	421	1.8% (0.9%-3.5%)	Small: 1.2% Large: 2.0% (0.5971)

Oral solutions	421	4.5% (2.9%-6.9%)	Small: 3.0% Large: 5.1% (0.3564)
Otic solutions	421	0.5% (0.1%-1.7%)	Small: 0.6% Large: 0.4% (0.7669)

Percentage of hospitals that obtained any of the following categories of NPS compounded drugs from outside compounding facilities

Drug	Sample Size	Point Estimate (95-Percent Confidence Intervals)	Independent Group T-Test By Hospital Size (P-Value)
Pitocin/oxytocin	421	57.6% (53.2%-62.0%)	Small: 32.1% Large: 67.9% (<0.0001)
Parenteral Nutrition	421	4.8% (3.1%-7.3%)	Small: 0.0% Large: 6.7% (0.0036)
Narcotics/controlled substances	421	74.9% (71.0%-78.4%)	Small: 53.3% Large: 83.5% (<0.0001)
Antiarrhythmic agents (e.g., amiodarone)	421	11.1% (8.5%-14.4%)	Small: 5.5% Large: 13.4% (0.0193)
Inotropic/vasopressors agents (e.g., dobutamine)	421	23.4% (19.6%-27.6%)	Small: 7.3% Large: 29.8% (<0.0001)
Cardioplegia	421	14.0% (11.0%-17.7%)	Small: 0.0% Large: 19.6 (<0.0001)
Antibiotics/antimicrobials	421	22.6% (18.9%-26.7%)	Small: 10.3% Large: 27.5% (0.0001)
Radiopharmaceuticals	421	5.2% (3.5%-7.8%)	Small: 3.6% Large: 5.9% (0.3511)

Nerve blocks	421	14.6% (11.5%-18.2%)	Small: 7.9% Large: 17.3% (0.0136)
Electrolyte solutions	421	12.3% (9.5%-15.8%)	Small: 1.8% Large: 16.5% (<0.0001)
Dialysis fluid and drugs (e.g., continuous renal replacement therapy, continuous veno-venous hemofiltration)	421	2.5% (1.4%-4.6%)	Small: 0.0% Large: 3.5% (0.0366)
Oncology drugs	421	0.7% (0.2%-2.2%)	Small: 0.6% Large: 0.8% (0.8469)
Non-chemo hazardous drugs	421	5.1% (3.3%-7.7%)	Small: 1.2% Large: 6.7% (0.0214)
Anesthetic agents	421	16.3% (13.1%-20.0%)	Small: 10.9% Large: 18.4% (0.0590)
Anesthesia syringes (neuromuscular blockers)	421	44.7% (40.2%-49.3%)	Small: 27.3% Large: 51.7% (<0.0001)
Diagnostic testing reagents	421	2.0% (1.0%-3.9%)	Small: 0.0% Large: 2.7% (0.0662)
Compounded topical medications	421	9.8% (7.4%-12.9%)	Small: 10.9% Large: 9.4% (0.6409)

APPENDIX B: Types of drugs compounded in hospital pharmacies on a non-patient-specific basis

Percentage of hospitals that compounded NPS drugs with the following characteristics in their pharmacies

Drug	Sample Size	Point Estimate (95-Percent Confidence Intervals)	Independent Group T-Test By Hospital Size (P-Value)
High-volume compounded sterile preparations	428	24.0% (20.3%-28.2%)	Small: 6.8% Large: 31.5% (<0.0001)
Low-volume compounded sterile preparations	428	22.8% (19.1%-26.9%)	Small: 11.9% Large: 27.5% (0.0004)
High-risk compounded sterile preparations	428	3.8% (2.3%-6.1%)	Small: 0.6% Large: 5.2% (0.0214)
Products in shortage	428	22.3% (18.6%-26.4%)	Small: 8.5% Large: 28.3% (<0.0001)
Emergency cart medications	428	4.7% (3.0%-7.2%)	Small: 1.7% Large: 6.0% (0.0546)
Research/study drugs	428	0.6% (0.1%-2.0%)	Small: 0.0% Large: 0.8% (0.3087)

Percentage of hospitals that compounded NPS drugs with the following mode of delivery or dosage form type

Drug	Sample Size	Point Estimate (95-Percent Confidence Intervals)	Independent Group T-Test By Hospital Size (P-Value)
Operating room syringes	428	15.2% (12.1%-18.9%)	Small: 5.1% Large: 19.6% (0.0001)
Patient-controlled analgesia	428	19.1% (15.6%-23.0%)	Small: 5.1% Large: 25.1% (<0.0001)
Epidurals	428	14.8% (11.8%-18.5%)	Small: 4.0% Large: 19.6% (<0.0001)
Critical care infusions	428	10.7% (8.1%-14.1%)	Small: 0.6% Large: 15.2% (<0.0001)
Intrathecals	428	0.6% (0.1%-2.0%)	Small: 0.0% Large: 0.8% (0.3087)
Eye drops	428	3.9% (2.4%-6.2%)	Small: 1.7% Large: 4.8% (0.1289)
Creams/ointments/suppositories or other topical agents	428	14.2% (11.2%-17.8%)	Small: 10.2% Large: 15.9% (0.1207)
Tablets/capsules	428	0.9% (0.3%-2.3%)	Small: 1.1% Large: 0.8% (0.7285)
Oral solutions	428	23.0% (19.3%-27.2%)	Small: 11.9% Large: 27.9% (0.0003)
Otic solutions	428	0.7% (0.2%-2.1%)	Small: 0.6% Large: 0.8% (0.7988)

Percentage of hospitals that compounded any of the following categories of NPS drugs

Drug	Sample Size	Point Estimate (95-Percent Confidence Intervals)	Independent Group T-Test By Hospital Size (P-Value)
Pitocin/oxytocin	428	23.2% (19.5%-27.4%)	Small: 9.7% Large: 29.1% (<0.0001)
Parenteral Nutrition	428	3.1% (1.8%-5.3%)	Small: 0.0% Large: 4.4% (0.0153)
Narcotics/controlled substances	428	20.7% (17.1%-24.7%)	Small: 6.8% Large: 26.7% (<0.0001)
Antiarrhythmic agents (e.g., amiodarone)	428	2.5% (1.4%-4.6%)	Small: 0.0% Large: 3.6% (0.0279)
Inotropic/vasopressors agents (e.g., dobutamine)	428	6.4% (4.4%-9.2%)	Small: 0.0% Large: 9.2% (0.0003)
Cardioplegia	428	5.5% (3.7%-8.2%)	Small: 0% Large: 8.0% (0.0009)
Antibiotics/antimicrobials	428	23.3% (19.6%-27.5%)	Small: 7.4% Large: 30.3% (<0.0001)
Radiopharmaceuticals	428	0.0% (0.0%-1.8%)	Small: 0% Large: 0% (N/A)
Nerve blocks	428	4.2% (2.7%-6.6%)	Small: 1.1% Large: 5.6% (0.0359)
Electrolyte solutions	428	7.5% (5.3%-10.5%)	Small: 0.0% Large: 10.8% (<0.0001)

Dialysis fluid and drugs (e.g., continuous renal replacement therapy, continuous veno-venous hemofiltration)	428	0.3% (0.04%-1.8%)	Small: 0.0% Large: 0.4% (0.4724)
Oncology drugs	428	0.6% (0.1%-2.0%)	Small: 0.0% Large: 0.8% (0.3087)
Non-chemo hazardous drugs	428	2.8% (1.5%-4.9%)	Small: 0.0% Large: 4.0% (0.0210)
Anesthetic agents	428	4.6% (3.0%-7.1%)	Small: 0.6% Large: 6.4% (0.0084)
Anesthesia syringes (neuromuscular blockers)	428	3.9% (2.4%-6.2%)	Small: 1.7% Large: 4.8% (0.1289)
Diagnostic testing reagents	428	0.6% (0.1%-2.0%)	Small: 0% Large: 0.8% (0.3087)
Compounded topical medications	428	14.1% (11.2%-17.7%)	Small: 9.1% Large: 16.3% (0.0482)

APPENDIX C: Types of drugs that hospitals reported being unable to obtain on a non-patient-specific basis

Percentage of hospitals that were unable to obtain NPS compounded drugs with the following characteristics from outside compounders

Drug	Sample Size	Point Estimate (95-Percent Confidence Intervals)	Independent Group T-Test By Hospital Size (P-Value)
High-volume compounded sterile preparations	223	58.6% (52.3%-64.6%)	Small: 41.7% Large: 61.5% (0.0164)
Low-volume compounded sterile preparations	223	51.2% (44.9%-57.5%)	Small: 41.7% Large: 52.8% (0.1731)
High-risk compounded sterile preparations	223	16.9% (12.6%-22.3%)	Small: 8.3% Large: 18.4% (0.1585)
Products in shortage	223	76.3% (70.7%-81.1%)	Small: 52.1% Large: 80.5% (0.0006)
Emergency cart medications	223	25.7% (20.5%-31.6%)	Small: 14.6% Large: 27.6% (0.1176)
Research/study drugs	223	0.3% (0.05%-1.8%)	Small: 2.1% Large: 0.0% (0.0464)

Percentage of hospitals that were unable to obtain NPS compounded drugs with the following mode of delivery or dosage form type from outside compounders

Drug	Sample Size	Point Estimate (95-Percent Confidence Intervals)	Independent Group T-Test By Hospital Size (P-Value)
Operating room syringes	223	44.2% (38.1%-50.6%)	Small: 27.1% Large: 47.2% (0.0329)
Patient-controlled analgesia	223	49.5% (43.3%-55.8%)	Small: 33.3% Large: 52.3% (0.0451)
Epidurals	223	34.5% (28.8%-40.8%)	Small: 31.3% Large: 35.1% (0.6711)
Critical care infusions	223	24.3% (19.3%-30.2%)	Small: 8.3% Large: 27.1% (0.0212)
Intrathecals	223	1.3% (0.4%-3.8%)	Small: 2.1% Large: 1.2% (0.6772)
Eye drops	223	2.3% (1.0%-5.2%)	Small: 2.1% Large: 2.3% (0.9398)
Creams/ointments/suppositories or other topical agents	223	1.1% (0.4%-3.2%)	Small: 4.2% Large: 0.6% (0.0696)
Tablets/capsules	223	0.5% (0.1%-3.1%)	Small: 0.0% Large: 0.6% (0.6659)
Oral solutions	223	1.6% (0.6%-4.0%)	Small: 4.2% Large: 1.2% (0.2046)
Otic solutions	223	0.0% (0.0%-3.4%)	Small: 0.0% Large: 0.0% (N/A)

Percentage of hospitals unable to obtain NPS compounded drugs in the following categories from outside compounders

Drug	Sample Size	Point Estimate (95-Percent Confidence Intervals)	Independent Group T-Test By Hospital Size (P-Value)
Pitocin/oxytocin	223	48.1% (41.9%-54.5%)	Small: 37.5% Large: 50.0% (0.1892)
Parenteral Nutrition	223	1.8% (0.7%-4.5%)	Small: 2.1% Large: 1.7% (0.8763)
Narcotics/controlled substances	223	61.6% (55.3%-67.4%)	Small: 41.7% Large: 65.0% (0.0050)
Antiarrhythmic agents (e.g., amiodarone)	223	8.9% (5.9%-13.3%)	Small: 4.2% Large: 9.8% (0.3026)
Inotropic/vasopressors agents (e.g., dobutamine)	223	16.9% (12.6%-22.3%)	Small: 8.3% Large: 18.4% (0.1585)
Cardioplegia	223	5.4% (3.1%-9.2%)	Small: 0.0% Large: 6.3% (0.1410)
Antibiotics/antimicrobials	223	21.8% (17.0%-27.6%)	Small: 8.3% Large: 24.1% (0.0437)
Radiopharmaceuticals	223	1.5% (0.5%-4.2%)	Small: 0.0% Large: 1.7% (0.4521)
Nerve blocks	223	7.6% (4.9%-11.7%)	Small: 8.3% Large: 7.5% (0.8478)
Electrolyte solutions	223	18.9% (14.4%-24.4%)	Small: 8.3% Large: 20.7% (0.0966)

Dialysis fluid and drugs (e.g., continuous renal replacement therapy, continuous veno-venous hemofiltration)	223	1.0% (0.3%-3.6%)	Small: 0.0% Large: 1.2% (0.5404)
Oncology drugs	223	0.3% (0.1%-1.8%)	Small: 2.1% Large: 0.0% (0.0464)
Non-chemo hazardous drugs	223	2.0% (0.8%-4.9%)	Small: 0.0% Large: 2.3% (0.3840)
Anesthetic agents	223	11.5% (8.0%-16.2%)	Small: 8.3% Large: 12.1% (0.5396)
Anesthesia syringes (neuromuscular blockers)	223	31.1% (25.5%-37.2%)	Small: 14.6% Large: 33.9% (0.0277)
Diagnostic testing reagents	223	1.0% (0.3%-3.6%)	Small: 0.0% Large: 1.2% (0.5404)
Compounded topical medications	223	1.1% (0.4%-3.2%)	Small: 4.2% Large: 0.6% (0.0696)

APPENDIX D: Point estimates and confidence intervals for findings

Finding	Sample Size	Point Estimate (95-Percent Confidence Intervals)
Hospitals that obtained non-patient-specific drugs only from facilities registered with FDA as 503B outsourcing facilities (among hospitals that obtained non-patient-specific drugs from outside compounders)	389	88.9% (86.1%-91.3%)
Hospitals that obtained non-patient-specific drugs from unregistered facilities and facilities registered with FDA as 503B outsourcing facilities (among hospitals that obtained non-patient-specific drugs from outside compounders)	389	9.3% (7.1%-12.0%)
Hospitals that obtained non-patient-specific drugs only from unregistered facilities (among hospitals that obtained non-patient-specific drugs from outside compounders)	389	1.8% (1.0%-3.1%)
Hospitals that obtained non-patient-specific drugs from more than one outside compounder (among hospitals that obtained non-patient-specific drugs from outside compounders)	389	55.8% (51.7%-59.9%)
Hospitals that obtained non-patient-specific drugs from between one and	389	88.7% (85.7%-91.1%)

three outside compounders (among hospitals that obtained non-patient-specific drugs from outside compounders)		
Hospitals that faced challenges in obtaining all the non-patient-specific drugs they sought from outside compounders (among all hospitals)	563	44.8% (41.1%-48.5%)
Hospitals that considered or were currently considering registering their pharmacies as 503B outsourcing facilities (among hospitals that compounded drugs in their own pharmacies)	428	1.7% (0.7%-4.2%)
Hospitals that obtained non-patient-specific compounded drugs from at least one outside compounder and also compounded them in their own pharmacies (among hospitals that compounded non-patient-specific drugs in-house and/or obtained them from outside compounders)	426	47.2% (42.8%-51.8%)
Hospitals that relied solely on their pharmacies for non-patient-specific compounded drugs (among hospitals that compound non-patient-specific drugs in-house and/or obtain them from outside compounders)	426	8.1% (6.0%-10.1%)

APPENDIX E: Factors that hospitals considered when choosing where to obtain compounded drugs

Factor	Sample Size	Point Estimate (95% Confidence Intervals)
History of State actions against facility (e.g., suspension or revocation of State license)	421	94.1% (91.7%-95.8%)
History of Federal enforcement actions against facility (e.g., seizure or injunction)	421	94.0% (91.6%-95.7%)
History of product recalls and/or cessation of sterile operations	421	92.1% (89.4%-94.1%)
Quality assurance documentation	421	91.6% (88.9%-93.8%)
Registration status with FDA as a 503B outsourcing facility	421	91.5% (88.8%-93.6%)
Facility's accreditation status	421	90.6% (87.6%-92.9%)
Appropriate licensure of pharmacy staff	421	89.7% (86.7%-92.1%)
Warning letters issued based on FDA inspection findings	421	87.1% (83.7%-89.8%)
Facility's reputation	421	85.9% (82.5%-88.8%)

Facility's ability to produce a specific product	421	84.9% (81.3%-87.9%)
Facility's ability to produce products with extended beyond use dates/expiration dates	421	78.7% (74.8%-82.1%)
Staff training and competency assessment documentation	421	75.3% (71.2%-79.0%)
Observations listed on FDA Form 483	421	69.8% (65.5%-73.8%)
Cost of products	421	58.3% (53.7%-62.7%)
Hospital contract with group purchasing organization	421	53.2% (48.6%-57.7%)
Hospital's history of purchasing from facility	421	48.9% (44.3%-53.5%)

APPENDIX F: Agency Comments

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

DATE: May 6, 2019

TO: Daniel R. Levinson
Inspector General

FROM: Lisa Rovin, JD
Director, Office of Public Health Strategy and Analysis

SUBJECT: Food and Drug Administration's Response to Office of Inspector General Draft Report: Most Hospitals Obtain Compounded Drugs from Outsourcing Facilities, Which Must Meet FDA Quality Standards, OEI-01-17-00090

The Food and Drug Administration (FDA) appreciates the opportunity to review and comment on the Office of Inspector General's (OIG) draft report entitled, "Most Hospitals Obtain Compounded Drugs from Outsourcing Facilities, Which Must Meet FDA Quality Standards, OEI-01-17-00090."

Lisa Rovin

Attachment

Food and Drug Administration's General Comments to

Office of Inspector General's Draft Report

"Most Hospitals Obtain Compounded Drugs from Outsourcing Facilities, Which Must Meet FDA Quality Standards, OEI-01-17-00090"

The Food and Drug Administration (FDA) thanks the Office of Inspector General (OIG) for it's ongoing work on the topic of drug compounding, including this most recent report on hospital sourcing of supplies of non-patient-specific (NPS) compounded drugs. Although compounded drugs can serve an important medical need for certain patients, they also present a risk to patients. FDA's compounding program aims to protect patients from unsafe, ineffective, and poor-quality compounded drugs, while preserving access to compounded drugs for patients who have a medical need for them. Establishing policy, engaging stakeholders, and conducting risk-based oversight of drug compounding are Agency priorities. FDA believes the information contained in this report will be useful to FDA, hospitals, and other stakeholders with interests in drug compounding.

Response to OIG Recommendations

Recommendation 1: FDA should further communicate to hospitals the importance of obtaining NPS compounded drugs from registered outsourcers.

FDA concurs with this recommendation. The Agency is pleased to see that OIG found that most hospitals that need non-patient-specific compounded drugs source them from outsourcing facilities but agrees that ongoing outreach remains important. FDA regularly engages with hospital and health-system stakeholders regarding drug compounding and applicable law and policy, including at annual listening sessions which will occur again in June of 2019. FDA intends to continue these efforts. In addition, FDA continues to develop policy on compounding in the hospital and health-system setting, which will provide additional clarity to these entities. FDA will continue to post information about oversight actions relevant to outsourcing facilities on its website, and information provided by outsourcing facilities about the products they have recently produced, which may include drugs that have been or are in shortage.[1] FDA believes these tools have and will continue to inform hospital considerations about sourcing products from outsourcing facilities.

Recommendation 2: FDA should take appropriate follow up action on the list of unregistered compounding facilities provided.

FDA concurs with this recommendation. We thank OIG for providing FDA with a list of compounders that appear to be providing hospitals with non-patient-specific compounded drugs and that are not registered with FDA as outsourcing facilities. We have conducted inspections of a number of these sites already and have confirmed distribution of non-patient-specific compounded drugs in some cases. These inspections have identified objectionable conditions to

[1] Federal law requires that outsourcing facilities report to FDA whether they intend to compound drugs in shortage, but not which shortage drugs they intend to make. However, if outsourcing facilities have produced specific drugs in shortage, their historical product reports, available online, would contain this information.

some degree, and some have led to a recall. FDA will continue to take appropriate follow up actions with regard to these firms.

ACKNOWLEDGMENTS

Jesse Valente served as the team leader for this study, and Matt Blackburn served as the lead analyst. Office of Evaluation and Inspections staff who provided support include Althea Hosein, Christine Moritz, Michael Novello, and Melicia Seay.

This report was prepared under the direction of Joyce Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston regional office, and Kenneth Price, Deputy Regional Inspector General.

To obtain additional information concerning this report or to obtain copies, contact the Office of Public Affairs at Public.Affairs@oig.hhs.gov.

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Endnotes

[1] CDC, *Multistate Outbreak of Fungal Meningitis and Other Infections*. Accessed at http://www.cdc.gov/hai/outbreaks/meningitis.html on January 20, 2017.

[2] Drug Quality and Security Act, P.L. No. 113-54 (enacted Nov. 27, 2013).

[3] An "outsourcing facility" is a facility at one geographic location or address that (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all the requirements of section 503B of the FD&C Act. Section 503B(d)(4) of the FD&C Act.

[4] Section 503(b)(4) of the FD&C Act.

[5] FDA, *FDA's Human Drug Compounding Progress Report: Three Years After Enactment of the Drug Quality and Security Act*, January 2017. Accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM536549.pdf on January 23, 2017.

[6] Section 503B(b)(1)(B)(ii) of the FD&C Act. FDA, *Registered Outsourcing Facilities*. Accessed at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm on January 23, 2017.

[7] Section 503B(b)(1)(A) of the FD&C Act.

[8] OIG, *Memorandum Report: High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals That Use Them*, OEI-01-13-00150, April 2013.

[9] FDA, letter to hospitals regarding registered outsourcing facilities. Accessed at https://web.archive.org/web/20140630095703/http:/www.fda.gov:80/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM380599.pdf on June 26, 2018.

[10] FDA, *FDA's Human Drug Compounding Progress Report: Three Years After Enactment of the Drug Quality and Security Act*, January 2017. Accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM536549.pdf on May 18, 2017.

[11] Section 102 of Drug Quality and Security Act, adding section 503B to the FD&C Act.

[12] Section 503B(a) of the FD&C Act.

[13] FDA's regulations regarding CGMP requirements for the preparation of drug products are established in 21 CFR pts. 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. Until those regulations are finalized, outsourcing facilities are subject to 21 CFR pts. 210 and 211. FDA, *Draft Guidance for Industry: Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (Revision 1)*, December 2018. Accessed at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm403496.pdf on January 30, 2017.

[14] FDA, *Information Concerning Outsourcing Facility Registration*. Accessed at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm389118.htm#10 on March 2, 2017.

[15] FDA, *Registered Outsourcing Facilities*. Accessed at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm on January 23, 2017.

[16] FDA, *FDA's Human Drug Compounding Progress Report: Three Years After Enactment of the Drug Quality and Security Act*, January 2017. Accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM536549.pdf on January 23, 2017.

[17] FDA, *FDA Form 483 Frequently Asked Questions*. Accessed at http://www.fda.gov/ICECI/Inspections/ucm256377.htm on January 23, 2017.

[18] FDA, *Regulatory Procedures Manual*. Accessed at https://www.fda.gov/ICECI/compliancemanuals/regulatoryproceduresmanual/default.htm on May 18, 2017.

[19] FDA, *Draft Guidance for Industry: Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act*, April 2016. Accessed at

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496287.pdf on January 16, 2019.

[20]FDA, *2018 Compounding Policy Priorities*. Accessed at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm on February 27, 2018.

[21] FDA, *Draft Guidance for Industry: Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (Revision 1)*, December 2018. Accessed at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm403496.pdf on March 21, 2019.

[22] OIG, *High-Risk Compounded Sterile Preparations and Outsourcing by Hospitals That Use Them*, OEI-01-13-00150 (April 2013).

[23] OIG, *Compounded Drugs Under Medicare Part B: Payment and Oversight*, OEI-03-13-00270 (April 2014).

[24] OIG, *Medicare's Oversight of Compounded Drugs Used in Hospitals*, OEI-01-13-00400 (January 2015).

[25] The 95-percent confidence interval for this estimate is 77.3% to 82.4%.

[26] Five hospitals participated in a pre-test of our electronic questionnaire. We dropped these hospitals from the sampling frame for this study.

[27] We dropped one hospital from our sample at the request of OIG's Office of Investigations. We dropped four hospitals in Puerto Rico from our sample because of Hurricane Maria.

[28] OEI provided FDA with a list of outside compounding facilities identified by the hospitals that responded to our survey. Hospitals identified the outside compounding facilities from which they obtained compounded drugs in the year prior to the survey. We matched these hospital-identified outside compounding facilities with the compounding facilities that FDA's website listed as registered outsourcing facilities as of January 2, 2018. Hospitals also identified whether the outside compounding facilities provided them with patient-specific and/or non-patient-specific compounded drugs.

[29] According to FDA, it prioritizes drugs for its drug shortage list that are "medically necessary," meaning that they are used to treat or prevent serious diseases or medical conditions for which no alternative drugs, available in adequate supply, are acceptable substitutes. FDA, *Report on Drug Shortages for Calendar Year 2016, Required by Section 1002 of the Food and Drug Administration Safety and Innovation Act*. Accessed at https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM561290.pdf on May 30, 2018.

[30] FDA, *Guidance for Industry: Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, January 2018. Accessed at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM510153.pdf on January 16, 2019.

[31]ASHP (formerly the American Society of Hospital Pharmacists) and the Pew Charitable Trusts, *2015 Pharmaceutical Compounding Roundtable: How can outsourcing facilities meet provider needs?* Accessed at https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/sterile-compounding/compounding-roundtable.ashx on March 1, 2017.

[32] FDA, *2018 Compounding Policy Priorities*. Accessed at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm on January 29, 2019.