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November 2016

DRUG COMPOUNDING

FDA HAS TAKEN STEPS TO IMPLEMENT COMPOUNDING LAW, BUT SOME STATES AND STAKEHOLDERS REPORTED CHALLENGES

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GAO-17-64

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FDA Has Taken Steps to Implement Compounding Law, but Some States and Stakeholders Reported Challenges

GAO Highlights

Highlights of GAO-17-64, a report to congressional committees

Why GAO Did This Study

Drug compounding is the process of combining, mixing, or altering ingredients to create a drug tailored to the needs of an individual patient. An outbreak of fungal meningitis in 2012 linked to contaminated compounded drugs raised concerns about state and federal oversight of drug compounding. The Drug Quality and Security Act, enacted in 2013, helped clarify FDA's authority and included a provision for GAO to report on drug compounding.

This report examines (1) the settings in which drugs are compounded, and the extent of drug compounding; (2) state laws and policies governing drug compounding, and how they are enforced; (3) communication between states and FDA, as well as among states, regarding drug compounding, and the associated challenges; and (4) steps FDA has taken to implement its responsibilities to oversee drug compounding, and challenges that have been reported with these efforts.

[redacted]

surveyed state

View GAO-17-64. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

GAO's survey of state pharmacy regulatory bodies found that drugs are compounded in a variety of health care settings, and some data are collected on the number of entities that compound drugs (drug compounders), but not the volume of compounded drugs. In addition to pharmacies, drug compounding settings include physicians' offices and outsourcing facilities—a new type of facility established by law in 2013, which can compound sterile drugs without patient-specific prescriptions and register with and are inspected by the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS). While FDA and some states collect data on drug compounders, only one state reported collecting data on the number of prescriptions or the volume of compounded drugs. In addition, states GAO surveyed and stakeholders GAO interviewed did not collect data specific to the extent of compounding performed by nonpharmacists, such as physicians.

Nearly all of the states GAO surveyed reported having drug compounding laws, regulations, or policies, though few apply to nonpharmacists, and states conduct inspections and can take actions to enforce them. Less than 20 percent of states reported having laws, regulations, or policies specific to compounding by nonpharmacists (e.g., physicians), and these state laws varied. To help ensure compliance, most states reported inspecting drug compounders, such as pharmacies and outsourcing facilities, and most states can take several types of actions against pharmacies, including monetary fines, and suspension and revocation of a license or registration.

Most states reported being satisfied with their communication with FDA and other states, although some reported challenges. About three quarters of the states reported participating in FDA-sponsored activities, such as intergovernmental meetings, and obtaining information from FDA's website. Some states reported challenges with this communication, such as getting FDA to respond to requests for information. In terms of communication between states, most survey respondents reported that they are satisfied with this communication, which occurs through conferences and other activities.

FDA has taken steps to implement its regulatory responsibilities to oversee drug compounding, but states and stakeholder organizations have cited challenges and concerns. FDA has issued numerous draft and final guidance documents related to drug compounding, and conducted more than 300 inspections of drug compounders, which resulted in actions such as FDA issuing warning letters and voluntary recalls of potentially contaminated compounded drugs. Some stakeholder organizations said the amount of time it takes FDA to finalize the guidance and other documents—including those required by the 2013 law—is challenging. FDA officials noted that reviewing the large number of comments received has contributed to the time the agency has taken to finalize them. States and stakeholder organizations also cited concerns related to access to compounded drugs and differences between states and FDA on the appropriate inspection protocols to use when inspecting drug compounders. In August 2016,FDA changed its procedures to address concerns about the appropriate protocols to use for these inspections

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Abbreviations

CGMP	current good manufacturing practice
DQSA	Drug Quality and Security Act
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
HHS	Department of Health and Human Services
MOU	memorandum of understanding
USP	U.S. Pharmacopeial Convention

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November 17, 2016

The Honorable Lamar Alexander
Chairman
The Honorable Patty Murray
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Fred Upton
Chairman
The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce
House of Representatives

Drug compounding is the process of combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient. Compounding is typically used to prepare medications that are not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced pharmaceutical product. At the state level, drug compounding has traditionally been overseen by state pharmacy regulatory bodies (e.g., boards of pharmacy). In addition to pharmacists, other health care practitioners, such as physicians, may prepare compounded drugs, and these practitioners are generally overseen by their respective state licensing agencies (e.g., state medical boards). At the federal level, the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), is responsible for overseeing the safety and quality of domestic and imported pharmaceutical products under the Federal Food, Drug, and Cosmetic Act (FDCA).[1]

Concerns have been raised that some pharmacies were going beyond traditional drug compounding for individual patients by compounding and selling large quantities of drugs to facilities in multiple states without meeting federal safety and other requirements applicable to new drugs.

[1]See 21 U.S.C. §§ 301 *et seq.*

Further, an outbreak of fungal meningitis in 2012 linked to contaminated compounded steroid injections, which resulted in over 60 deaths and hundreds of people getting ill, raised questions about the safety and quality of compounded drugs and concerns about state and federal oversight of drug compounding. In July 2013, we reported that FDA's oversight authority was unclear and recommended that Congress consider clarifying FDA's authority to oversee drug compounding.[2] The Drug Quality and Security Act (DQSA), enacted in November 2013, helped clarify FDA's authority to oversee drug compounding nationally and created a new category of compounders called outsourcing facilities—facilities that meet certain FDA requirements, including compounding sterile drugs, that register with and are inspected by FDA, and are allowed to compound drugs without patient-specific prescriptions. The act also included a provision for GAO to review drug compounding.[3] This report examines

1. the settings in which drugs are compounded, and the extent of drug compounding in each state;
2. state laws, regulations, and policies governing drug compounding, and how they are enforced;
3. how communication is conducted between states and FDA, as well as among states, regarding compounding, and any associated challenges; and
4. steps FDA has taken to implement its responsibilities to oversee drug compounding since enactment of the DQSA, and any challenges that have been reported with these efforts.

This report also includes an appendix that describes information about the safety and quality of compounded drugs that is available to purchasers of these drugs (e.g., hospitals, health systems, and patients). (See app. I.)

[2]See GAO, *Drug Compounding: Clear Authority and More Reliable Data Needed to Strengthen FDA Oversight*, GAO-13-702 (Washington, D.C.: July 31, 2013). We also reported on drug compounding in 2003; see GAO, *Prescription Drugs: State and Federal Oversight of Drug Compounding by Pharmacies,* GAO-04-195T (Washington, D.C.: Oct. 23, 2003).

[3]Pub. L. No. 113-54, tit. I, 127 Stat. 587 (2013).

To address our objectives, we administered a web-based survey to the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands.[4] We achieved a survey response rate of 93 percent: 50 of the 54 states completed the survey. The survey collected information from the states on the settings in which drug compounding occurs; available data on drug compounding in each state; state laws, regulations, and policies related to drug compounding; activities states have participated in related to drug compounding with FDA and other states; states' perspectives on communication with FDA and other states; and their perspectives on FDA's implementation of the DQSA, among other things.[5]

In addition, we interviewed officials from 25 stakeholder organizations that have a stake or an interest in drug compounding to obtain information on topics such as state laws, regulations, and policies on drug compounding; their perspectives on any challenges in communication between FDA and states, as well as among states, related to drug compounding; and their perspectives on FDA's implementation of the DQSA. We selected these stakeholder organizations to include national organizations representing (1) pharmacies and pharmacists, including those that compound drugs; (2) physicians, including those in medical specialties identified as compounding drugs; and (3) state boards of pharmacy and state medical boards; as well as experts in drug compounding, and an organization that conducted research related to drug compounding. We reviewed relevant documents provided by these stakeholder organizations, including comments submitted to FDA regarding FDA's compounding-related activities. In addition to officials from the 25 stakeholder organizations, we interviewed state officials, including officials from the boards of pharmacy, medical boards, and the agencies that have oversight responsibility for outsourcing facilities in three selected states—North Carolina, Minnesota, and Texas. We selected these states because they reported differing laws, regulations, or policies related to drug compounding (such as oversight of outsourcing facilities) in their responses to the survey, among other reasons. We obtained information on state laws, regulations, and policies related to drug compounding in each selected state, and we

[4]We refer to all of the state pharmacy regulatory bodies that we surveyed as states in this report.

[5]Not all of the 50 respondents that completed the survey answered every survey question.

obtained additional details for certain survey responses from the board of pharmacy officials. In addition, we interviewed officials from two pharmacy benefit managers—third-party administrators of prescription drug programs for certain health plans and federal and state government employee plans—to obtain information related to drug compounding, including how these entities determine the safety and quality of compounded drugs. We used information collected from our survey and obtained from the interviews and related documents to describe the information about the safety and quality of compounded drugs that is available to purchasers of these drugs. The perspectives of the officials from the 25 stakeholder organizations, three selected states, and two pharmacy benefit managers are not generalizable, but provided us with valuable insight on these issues.

We interviewed FDA officials to obtain information on steps FDA has taken to implement its regulatory responsibilities to oversee drug compounding since enactment of the DQSA, and we reviewed relevant laws and regulations related to drug compounding. In addition, we reviewed relevant documents from FDA, including FDA's draft memorandum of understanding (MOU) with states regarding distribution of compounded human drug products, and FDA's draft and final guidance related to drug compounding and implementation of the DQSA, such as FDA's final guidance on registration of outsourcing facilities. We also analyzed FDA data on inspections of drug compounders, and data on actions taken, such as the issuance of warning letters related to drug compounding.[6] We determined that the data we used from FDA on inspections and actions taken related to drug compounding were sufficiently reliable for purposes of this study by discussing data collection processes and limitations of the data with agency officials, and comparing the data against other published sources. See appendix II for more detailed information on our objectives, scope, and methodology.

We conducted this performance audit from May 2015 to November 2016 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our

[6]An FDA warning letter is a correspondence that notifies a responsible individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the FDCA, its implementing regulations, and other federal statutes.

findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Traditionally, drug compounding is the process of combining, mixing, or altering ingredients to create a customized medication for an individual patient. For example, a pharmacist may tailor a medication for a patient who is allergic to an ingredient in a conventionally manufactured drug or prepare a liquid formulation for a patient who has difficulty swallowing pills. Pharmacies sometimes compound drugs in advance of receiving individual patient prescriptions in anticipation of receiving prescriptions based on historical prescribing patterns—a practice referred to as anticipatory compounding. Drugs are also sometimes compounded to be kept in stock by a hospital, clinic, or physician's office to administer to patients, such as patients with an immediate need for the compounded drug—a practice referred to as office-use compounding. In addition to pharmacists, other health care practitioners, such as physicians, may also compound drugs. Compounded drugs include nonsterile preparations—such as capsules, ointments, creams, gels, and suppositories—and sterile preparations, including intravenously administered fluids, ophthalmic products, and other injectable drugs. Compounded sterile drugs pose special risks of contamination if not made properly, and require special safeguards to prevent injury or death to patients receiving them. In addition, nonsterile drugs that are compounded improperly (e.g., if they contain too much active ingredient) can also cause serious harm.

An outbreak of fungal meningitis in 2012 linked to contaminated compounded drugs led to questions about the safety and quality of compounded drugs, and raised concerns about state and federal oversight of drug compounding. At the time, concerns were raised by FDA and others—including members of Congress and public health advocates—that some pharmacies were going beyond traditional drug compounding by producing large quantities of compounded drugs without prescriptions for individual patients, and selling those compounded drugs to facilities in multiple states. Many believed that these types of pharmacies were engaging in conventional manufacturing under the guise of compounding without meeting safety and other requirements with which conventional drug manufacturers must comply. In July 2013, we

found that the authority of FDA to oversee drug compounding was unclear and this lack of clarity had resulted in gaps in oversight of drug compounding.[7] Specifically, two federal circuit court decisions had resulted in differing FDA authority in different parts of the country, and these inconsistent decisions contributed to challenges in FDA's ability to inspect and take enforcement action against entities engaging in drug compounding.

In November 2013, the DQSA was enacted to help clarify FDA's authority to oversee drug compounding. The act established a new type of facility, an outsourcing facility, that prepares sterile compounded drugs and which may compound drugs without patient-specific prescriptions.[8] These outsourcing facilities differ from drug compounders operating under section 503A of the FDCA, which exempts drugs compounded by a licensed pharmacist or licensed physician based on the receipt of a valid prescription, for an identified individual patient, and in accordance with certain other conditions, from three key provisions of the FDCA that are otherwise applicable.[9] The DQSA also removed certain provisions from section 503A of the FDCA that were found to be unconstitutional by the U.S. Supreme Court in 2002, and affirmed the validity of the remaining

[7]See GAO-13-702.

[8]Section 503B of the FDCA, as added by the DQSA, defines an outsourcing facility as a facility at one geographic location or address that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of section 503B. Outsourcing facilities must comply with current good manufacturing practice (CGMP) requirements and will be inspected by FDA according to a risk-based schedule. In addition, outsourcing facilities must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the drug products they compound.

[9]Compounded drug products meeting the requirements of section 503A are exempt from the following three requirements in the FDCA: the requirements to comply with CGMP requirements, label drugs with adequate directions for use, and have an FDA-approved new drug or abbreviated new drug application. References to sections 503A and 503B in this report are to sections 503A and 503B of the FDCA, as codified at 21 U.S.C. §§ 353a, 353b.

provisions in section 503A.[10] Table 1 outlines some of the requirements under section 503A, applicable to 503A compounders, and section 503B, applicable to outsourcing facilities.[11]

Table 1: Requirements Applicable to Drug Compounders under Sections 503A and 503B of the FDCA

	503A compounder[a]	503B outsourcing facility
Who may compound	Licensed pharmacist in a state-licensed pharmacy or federal facility, or licensed physician.	Licensed pharmacist or individual under the direct supervision of a licensed pharmacist in an outsourcing facility.
Type of drugs compounded	May compound nonsterile drugs or sterile drugs.	Must compound sterile drugs and may also compound nonsterile drugs.
Prescriptions	Compounding must be based on receipt of a valid prescription for an identified individual patient.[b]	Compounding may or may not be based on receipt of prescriptions for identified individual patients.
Registration with the Food and Drug Administration (FDA)	No registration requirement.	Must register with FDA and reregister annually.
Inspections	No requirement for FDA to inspect; while FDA may choose to inspect, a pharmacy's or physician's records may be exempt from inspection in certain cases.[c]	Inspected by FDA according to a risk-based schedule, based on the known safety risks of such outsourcing facilities.
Quality standards	Exempt from current good manufacturing practice (CGMP) requirements, but not from other quality requirements, such as the prohibition on preparing, packing, or holding drugs under insanitary conditions.[d]	Must comply with CGMP requirements, in addition to other quality requirements, such as the prohibition on preparing, packing, or holding drugs under insanitary conditions.[d]

[10]In 2001, the United States Court of Appeals for the Ninth Circuit struck down all of the advertising, promotion, and solicitation provisions of section 503A of the FDCA because those provisions violated the Free Speech Clause of the First Amendment. The court also held that, because these provisions could not be severed from the remainder of section 503A, all of section 503A was invalid. In 2002, the United States Supreme Court struck down the law's advertising, promotion, and solicitation restrictions without addressing whether the rest of section 503A remained law. See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002). For additional information on the history of FDA's authority over drug compounding and approach to oversight before enactment of the DQSA, see GAO-13-702.

[11]For purposes of this report, we use the term 503A compounder to refer to individuals or entities that are not outsourcing facilities that qualify for the exemptions under section 503A of the FDCA, including pharmacies, physicians, and federal facilities. Drug compounders that do not qualify for the exemptions under section 503A, and are not outsourcing facilities under section 503B, are regulated as conventional manufacturers and are subject to the provisions of the FDCA applicable to such manufacturers.

	503A compounder[a]	503B outsourcing facility
Labeling[e]	No labeling requirements.	Compounded medications must have a label that includes, among other things • the statement, “This is a compounded drug”; • the date that the drug was compounded and the expiration date; • the statement “Not for resale” and, where applicable, “Office Use Only”; • a list of active and inactive ingredients; and • the name, address, and phone number of the outsourcing facility.
Reporting of drugs compounded	No reporting requirements.	Must submit a report to FDA upon initial registration and twice per year, identifying the drugs compounded by the facility during the previous 6 months. For each drug, the report must include the following information • the active ingredient and its source; • the strength of the active ingredient per unit; • the dosage form and route of administration; • the package description; • the number of units produced; and • the National Drug Code number of the source drug or bulk active ingredient, if available.
Reporting of adverse events	No reporting requirements.	Must submit adverse event reports to FDA.
Fees	No fee requirements.	Must pay annual establishment fees and any applicable reinspection fees.
Compounded drugs that are essentially copies of commercial drugs	Must not compound regularly or in inordinate amounts drug products that are essentially a copy of a commercially available drug product.	Compounded drugs must not be essentially a copy of one or more approved drugs.
Bulk substances	Product is compounded using bulk drug substances that are (1) components of FDA-approved human drugs; (2) the subject of an applicable monograph; or (3) appear on a list developed by FDA.	Product is compounded using bulk drug substances that either appear on a list developed by FDA or are used to compound drugs that appear on FDA’s drug shortage list at the time of compounding, distribution, and dispensing.
Drugs that may not be compounded[f]	Must not compound a drug product that (1) appears on a list developed by FDA of drug products withdrawn or removed from the market for safety or efficacy reasons, or (2) appears on a list developed by FDA of drug products that present demonstrable difficulties for compounding.	Must not compound a drug product that (1) appears on a list developed by FDA of drug products withdrawn or removed from the market for safety or efficacy reasons or (2) appears on a list of drugs or categories of drugs that present demonstrable difficulties for compounding.

Source: GAO analysis of the Federal Food, Drug, and Cosmetic Act (FDCA). | GAO-17-64

Notes: Drug compounders may also be subject to additional requirements under the FDCA.

[a]503A compounders are individuals or entities that are not outsourcing facilities that qualify for the exemptions under section 503A of the FDCA, including pharmacies, physicians, and federal facilities. Drug compounders that do not qualify for the exemptions under section 503A, and are not outsourcing facilities under section 503B, are regulated as conventional manufacturers and are subject to the provisions of the FDCA applicable to such manufacturers.

[b]Compounding can take place after the 503A compounder receives the prescription, or in limited quantities before the 503A compounder receives a prescription, provided the compounding is based on a history of receiving valid prescription orders for the product.

[c]A pharmacy's records are exempt from FDA's inspection authority if the pharmacy is in compliance with any applicable local laws regulating the practice of pharmacy and medicine, regularly engages in dispensing drugs upon a prescription from a licensed practitioner, and does not manufacture, prepare or compound drugs for sale other than during the regular course of their business of dispensing or selling drugs at retail. Even if a pharmacy or physician is exempt from a records inspection, FDA has general inspection authority to inspect any facility in which drugs are manufactured, processed, packed, or held. 21 U.S.C. § 374.

[d]CGMP requirements provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210-211.

[e]Compounded drugs remain subject to labeling requirements in section 503(b) of the FDCA concerning dispensed prescription drugs, regardless of whether they are compounded by 503A compounders or 503B outsourcing facilities. 21 U.S.C. § 352(b).

[f]FDA is required to establish lists for each of these categories for 503A compounders and 503B outsourcing facilities.

While FDA is required to inspect outsourcing facilities, it does not routinely inspect 503A compounders, although it may in certain instances (e.g., in response to complaints).[12] In general, states regulate compounding as part of the practice of pharmacy and the state pharmacy regulatory bodies (e.g., boards of pharmacy) are responsible for oversight of the practice of pharmacy, which may include inspections of pharmacies that are 503A compounders. For example, a state board of pharmacy

[12]FDA inspections may result in FDA issuing inspection observation reports, which are called FDA form 483 inspection observation reports, and, in some cases, warning letters or other regulatory actions. An FDA form 483 inspection observation report is a report that is issued at the conclusion of an inspection when FDA investigators have observed conditions that, in their judgment, may constitute violations of the FDCA and related acts.

may inspect pharmacies that compound drugs for compliance with the U.S. Pharmacopeial Convention's (USP) compounding standards.[13]

Drugs Are Compounded in a Variety of Settings; FDA and Some States Collect Data on the Number of Drug Compounders, but Not the Volume of Compounded Drugs

Our survey of state pharmacy regulatory bodies found that drugs are compounded in a variety of pharmacy and other health care settings, including outsourcing facilities. While FDA and some states collect data on drug compounders, nearly all of the states reported that they did not collect data on the volume of compounded drugs.

Drugs Are Compounded in a Variety of Pharmacy and Other Health Care Settings

Our survey of state pharmacy regulatory bodies found that drugs, including sterile drugs, are compounded in a variety of pharmacy and other health care settings. Respondents in almost all of the states we surveyed reported that different types of pharmacies, such as retail and hospital pharmacies, were authorized to prepare sterile compounded drugs in their state. Respondents in most states also reported that FDA-registered outsourcing facilities were authorized to compound sterile drugs in their states; however, respondents in 5 states reported that these

[13]USP is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines, food ingredients, and dietary supplements. USP's current suite of General Chapters for compounding includes: Chapter <797> *Pharmaceutical Compounding—Sterile Preparations*, which provides procedures and requirements for compounding sterile preparations; Chapter <795> *Pharmaceutical Compounding—Nonsterile Preparations*, which provides guidance on applying good compounding practices in the preparation of nonsterile compounded formulations for dispensing and/or administration to humans or animals; and Chapter <1160>*—Pharmaceutical Calculations in Prescription Compounding,* among others. According to USP officials, USP's compounding chapters reference over 40 additional USP chapters. In addition to setting standards that affect compounding, USP—through the United States Pharmacopeia-National Formulary, a compendium of public pharmacopeial standards—provides monographs for drug articles, including ingredients used in compounded preparations, and monographs for the compounded preparations themselves, comprising standards of identity, quality, purity, strength, packaging, and labeling.

entities were not authorized to do so for reasons including that the state was still in the process of developing a state license for these entities. In addition, respondents in over half of the states reported that physicians' offices—both general practitioners' offices and medical specialty offices (e.g., dermatologists and pediatricians)—were authorized to prepare sterile compounded drugs in their states; however, respondents in several other states reported that they did not know if certain medical settings were authorized to do so. For example, respondents in 18 states reported that they did not know if general practitioners' offices were authorized. See table 2 for information on the types of entities authorized to prepare sterile compounded drugs.

Table 2: Types of Entities Authorized to Prepare Sterile Compounded Drugs, by Number of Reporting States

	Number of states (%)			
Type of entity	**Yes, authorized**	**No, not authorized**	**Don't know**	**No response**
Corporate chain pharmacies (e.g., Walgreens, CVS)	42 (84)	5 (10)	1 (2)	2 (4)
Retail pharmacies (e.g., independently owned pharmacies, community pharmacies, and compounding pharmacies that fill walk-in patient prescriptions)	45 (90)	2 (4)	0 (0)	3 (6)
Compounding pharmacies (e.g., large-scale pharmacies that do not fill walk-in patient prescriptions, and licensed in multiple states)	46 (92)	1 (2)	1 (2)	2 (4)
FDA-registered outsourcing facilities	39 (78)	5 (10)	4 (8)	2 (4)
Outsourcing facility (licensed or registered by state)	29 (58)	9 (18)	8 (16)	4 (8)
Hospital pharmacies	48 (96)	0 (0)	0 (0)	2 (4)
Outpatient clinics	33 (66)	4 (8)	11 (22)	2 (4)
Home infusion pharmacies	46 (92)	0 (0)	2 (4)	2 (4)
General practitioners' offices	26 (52)	4 (8)	18 (36)	2 (4)
Medical specialty offices (e.g., dermatologists, pediatricians)	26 (52)	5 (10)	18 (36)	1 (2)
Home health care agencies	15 (30)	11 (22)	22 (44)	2 (4)
Hospice and palliative care agencies	14 (28)	10 (20)	22 (44)	4 (8)

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Note: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

Respondents in several states reported that any licensed or registered pharmacy could potentially compound nonsterile drugs. For example, respondents in two states commented that almost all pharmacies compound or have the potential to compound nonsterile drugs, such as simple creams. A respondent in one state commented that they are under the assumption that any licensed pharmacy can perform nonsterile compounding without a special authorization to do so, and a respondent in another state reported that nearly all community and hospital pharmacies do at least some nonsterile compounding.

In addition, officials from some of the stakeholder organizations we interviewed said that certain medical specialists, such as dermatologists, pediatricians, and allergists, prepare compound drugs. They explained that, for example, some medical specialists mix nonsterile topical creams

or sterile preparations, such as lidocaine (a local anesthetic agent that can be administered by injection), as part of their medical practice. However, some of these officials said that whether health care practitioners compounded drugs depended on what was considered compounding, and that some medical specialists generally use compounded drugs provided by a pharmacy or outsourcing facility and do not compound the drugs themselves.

FDA and Some States Collect Data on Drug Compounders, but Only One State Reported Collecting Data on the Volume of Compounded Drugs

According to FDA officials, there is no good source for data on the extent of drug compounding and who is doing it except for data on outsourcing facilities. Although outsourcing facilities are required to provide FDA with a report of the drugs they compounded during the previous 6-month period, including the number of units they produced, aggregate data on the listed drugs were not available at the time of our review. According to FDA officials, not all outsourcing facilities provided these reports and the data provided were not yet collected and maintained in a standard format. Therefore, the officials said that FDA does not input the data into a single database, but instead maintains this information on the individual spreadsheets that the outsourcing facilities provided. According to FDA, the agency plans to makes necessary modifications to its electronic reporting system to accommodate the information outsourcing facilities must provide in the future so that outsourcing facilities will be able to electronically submit drug product reports into a single standardized format.[14] In addition, even though the compounded drugs are reported—and some outsourcing facilities report thousands of compounded drugs—FDA has not received data on the quantity of each drug listed in the reports in some cases, according to the officials. Further, while all outsourcing facilities are required to submit drug product reports to FDA, the officials we interviewed said that there are some facilities that have not provided it. As of April 22, 2016, 40 of the 59 outsourcing facilities had not provided some or all required reports. One FDA official said that to date, FDA has not taken regulatory action against outsourcing facilities

[14]FDA issued revised draft guidance on drug product reporting for outsourcing facilities in November 2014, and when this guidance is finalized it will prescribe the form and manner in which outsourcing facilities are required to submit drug reporting information to FDA. See Food and Drug Administration, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (Rockville, Md.: Nov. 2014).

that have not provided the reports of the drugs they compounded unless FDA was already taking steps to address some other violation of statute by the outsourcing facility, including through the issuance of a warning letter. According to the FDA officials, this is because addressing all of the firm's violations that FDA has identified in a single action is a more effective mechanism to bring the firm into compliance and a more efficient use of agency resources than pursuing separate actions for discrete violations of the FDCA.

While respondents in almost all of the states we surveyed reported having license categories for resident and nonresident pharmacies, respondents in some states reported having other license categories, including those specific to sterile drug compounding.[15] For example, 12 states reported having a separate license category for resident pharmacies that compound sterile drugs and 12 states reported having a sterile compounding license category for nonresident pharmacies. Other respondents reported licensing categories for pharmacies that included nuclear pharmacies, home infusion pharmacies, and Internet/mail order pharmacies; and entities that distribute compounded drugs.[16] (See table 3.) In addition, respondents in some states reported that they do not have separate license categories for specific types of practice settings; however, they are aware of pharmacies and other entities in their state that engage in certain practice areas (e.g., pharmacies that engage in sterile compounding).

[15]Resident pharmacies are those located within the state. Nonresident pharmacies are those located outside of the state.

[16]For example, a licensed wholesale distributor may distribute compounded drugs.

Table 3: State-Reported Categories of Licenses, Permits, or Registrations for Pharmacies and Other Entities, by State

	Number of states (%)		
Category of license, permit, or registration	**Yes**	**No**	**No response**
Resident pharmacies	50 (100)	0 (0)	0 (0)
Nonresident pharmacies	48 (96)	2 (4)[a]	0 (0)
Resident sterile compounding pharmacies	12 (24)	38 (76)	0 (0)
Nonresident sterile compounding pharmacies	12 (24)	38 (76)	0 (0)
Resident community pharmacy	22 (44)	27 (54)	1 (2)
Resident nuclear pharmacy	17 (34)	30 (60)	3 (6)
Resident long-term-care pharmacy	11 (22)	38 (76)	1 (2)
Resident hospital pharmacy	25 (50)	23 (46)	2 (4)
Resident home infusion pharmacy	7 (14)	41 (82)	2 (4)
Resident specialty pharmacy	8 (16)	40 (80)	2 (4)
Resident Internet or mail-order pharmacy	5 (10)	41 (82)	4 (8)
Nonresident Internet or mail-order pharmacy	11 (22)	35 (70)	4 (8)
Resident wholesale distributor[b]	41 (82)	7 (14)	2 (4)
Nonresident wholesale distributor[b]	36 (72)	10 (20)	4 (8)
Resident outsourcing facility	18 (36)	30 (60)	2 (4)
Nonresident outsourcing facility	15 (30)	31 (62)	4 (8)

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

[a]Two states reported that they have a pharmacy license, but not separate licenses for resident and nonresident pharmacies.

[b]Some states reported that they do not differentiate between resident and nonresident wholesale distributors, and some states reported that other state agencies, such as the department of health, oversee these entities.

In addition, respondents in half of the states we surveyed reported collecting data on licensed or registered pharmacies that compound sterile drugs, but not all of these states reported data.[17] For example, 16 states reported data for 2015, ranging from 31 pharmacies in Nevada to

[17]Thirty-two states reported that they did not differentiate data on pharmacies on drug compounding for human use versus drug compounding for animal (i.e., veterinary) use, 15 states reported they could differentiate some or all of the data, and 3 states did not respond to this survey question. Therefore, some of the data reported could include drug compounding for human and animal use.

1,024 in California. Respondents in most of the states that reported data on pharmacies that compound sterile drugs reported collecting this information yearly. (See table 4.)

Table 4: States That Reported Data on the Number of Licensed or Registered Resident and Nonresident Pharmacies That Compound Sterile Drugs, Calendar Year 2015

	Number of pharmacies that compound sterile drugs			
State	**All licensed or registered pharmacies**	**Resident pharmacies**	**Nonresident pharmacies**	**Frequency in which state collects this data**
California	1,024	935	89	Continuously updated[a]
Florida	581	456	125	Yearly[b]
Iowa	385	157	228	Yearly
Kansas[c]	269	109	160	Yearly
Kentucky	354	184	170	Yearly
Minnesota[c]	140	100	40	Not specified
Nevada[c]	31	31	—[d]	Not specified
New Jersey[c]	376	175	201	Yearly
North Carolina	448	263	185	Continuously updated
Ohio	352	94	258	Yearly
Oklahoma[c]	313	280	33	Yearly
South Carolina[c]	336	123	213	Yearly
South Dakota[c]	35	35	—[d]	Yearly
Texas	928	780	148	Yearly[e]
Virginia	321	162	159	Yearly[f]
Wyoming	146	5	141	Yearly

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

[a]California requires a special license for sterile compounding and reported the number of pharmacies with that license as of January 1, 2015.

[b]Florida reported 2015 data for the state's fiscal year, July 1, 2014, through June 30, 2015.

[c]These states reported estimated counts.

[d]Nevada and South Dakota reported that their states do not collect these data.

[e]Texas reported 2015 data as of September 8, 2015.

[f]Virginia reported 2015 data as of July 2, 2015.

National data on the extent of drug compounding, as measured by the number of prescriptions or the volume of compounded drugs (e.g., number of units), were not available from our survey, as only one state reported collecting these data, and its data were limited to sterile

compounded drugs. That state reported that 658,128 total prescriptions for sterile compounded drugs were dispensed by pharmacies in the state in 2014, and 708,142 total prescriptions were dispensed in 2015.[18] In addition, the state reported that close to 2.5 million units of sterile compounded drugs were dispensed by pharmacies in the state in 2014, and almost 2 million units were dispensed in 2015.[19] Staff from the state's board of pharmacy said that the state does not collect data on the total number of all prescriptions dispensed by pharmacies; therefore, they could not calculate the percentage of prescriptions for sterile compounded drugs to all prescription drugs. Board staff also noted that the source of the state's data was based on self-reporting from pharmacies; as such, pharmacies' methods for identifying and reporting numbers of prescriptions and units of sterile compounded drugs may differ, and the state cannot confirm the validity or accuracy of the data.

When asked if collecting data on the number of prescriptions for compounded drugs or the volume of compounded drugs would have any effect on their oversight of drug compounding activities, officials from the state boards of pharmacy in our three selected states said that collecting such data could be burdensome and costly. For example, the official from Texas said that because they have thousands of licensed pharmacies in their state, the volume of such data would be overwhelming and they do not know what they would do with all of that data. The official from North Carolina said that there would be a significant cost to collecting these data and the ultimate benefit is unclear. In addition, the official from Minnesota said that it seemed like there could be a sizable amount of data to collect, and the pharmacy board would have to work out details, including whether the data would be collected in aggregate or much more specifically by patient, how the data would be collated and stored (such as in a database), and how the board would pay for such data collection and management.

[18]According to staff from the state's board of pharmacy, these data only include sterile compounded drugs dispensed by a pharmacy, and do not include sterile compounded drugs dispensed by other health care practitioners, such as physicians, or nonsterile compounded drugs.

[19]This state defines a unit of compounded drug dispensed as a single dosage vial or package.

Officials in almost all of the stakeholder organizations we interviewed had not conducted or were not aware of any studies or reviews on the extent of drug compounding or the settings in which compounding occurs in each state. However, one stakeholder organization, the Pew Charitable Trusts, conducted a survey of the state boards of pharmacy in the 50 states and the District of Columbia (43 of the 51 states responded) on state oversight of sterile drug compounding.[20] Among its findings, the Pew Charitable Trusts reported that from 3 percent to 24 percent of pharmacies in the 43 responding states were performing sterile compounding. In June 2016, HHS's Office of Inspector General reviewed spending for compounded drugs under Part D, the Medicare program's prescription drug benefit.[21] This review found that Medicare Part D spending for compounded drugs rose from $70.2 million in 2006 to $508.7 million in 2015, particularly for topical compounded drugs which include creams and ointments. The HHS Office of Inspector General attributed this increase to both an increase in the average cost of prescriptions and an increase in the number of beneficiaries receiving these compounded drugs.

While respondents in 26 states reported that providers in general practitioners' and medical specialty offices were authorized to compound drugs in their state, we did not find any sources of data specific to the extent to which this occurs. In one of our selected states, the state medical board official said that the extent of drug compounding by physicians and nonpharmacist health care practitioners is likely minimal because their board has not heard about it; however, because the board is complaint driven (i.e., they only inspect or investigate practitioners if a complaint has been submitted) it could be that such compounding activity has not led to any complaints. Another state's medical board official told us that it is not known whether the scale of compounding by physicians is small and specific to certain medical specialties, or whether it is widespread. This official speculated that it is not widespread, except

[20]The Pew Charitable Trusts, *National Assessment of State Oversight of Sterile Drug Compounding* (Washington D.C.: February 2016). The Pew Charitable Trusts also reported on best practices related to drug compounding; see The Pew Charitable Trusts, *Best Practices for State Oversight of Drug Compounding* (Washington D.C.: March 2016).

[21]Department of Health and Human Services, Office of Inspector General, *High Part D Spending on Opioids and Substantial Growth in Compounded Drugs Raise Concerns* (Washington D.C.: June 2016).

within particular medical specialties. Further, officials from one stakeholder organization—a national medical association—said that they were not sure how extensive compounding by physicians is or the amount of compounding that is being conducted; and officials from another stakeholder organization—a different national medical association—told us that they would not know how to go about gathering information on the extent of compounding by physicians. Finally, an official from another stakeholder organization—a national pharmacy association—told us the extent of physician compounding varies dramatically depending on the practice environment or physician specialty, in that almost every patient receives compounded drugs from physicians in outpatient surgery and cancer centers, but general practitioners do not usually perform much compounding otherwise.

Nearly All States Reported Having Drug Compounding Laws, Though Few Apply to Nonpharmacists, and States Conduct Inspections and Can Take Actions to Enforce These Laws

Respondents in almost all of the states we surveyed reported having laws, regulations, or policies specific to the practice of drug compounding. However, few apply to physicians and other nonpharmacists. To help ensure compliance with state laws, regulations, or policies specific to drug compounding, respondents in most states reported inspecting pharmacies and other drug compounders, and most reported their state can take several types of actions against noncompliant pharmacies or other drug compounders.

Almost All States Reported Having Laws, Regulations, or Policies Specific to Drug Compounding

Respondents in 48 of the states we surveyed reported having laws, regulations, or policies specific to the practice of drug compounding; however, these generally only apply to pharmacies and pharmacists. A respondent in one of the remaining states—Pennsylvania—reported that its state had proposed rules and regulations governing compounding

practices.[22] The respondent in the other remaining state—New York—reported that the state did not have any laws specific to compounding; however, the state had laws regarding outsourcing facilities operating under section 503B of the FDCA. Respondents in over half the states (26) reported enacting laws or adopting regulations or policies specific to drug compounding in response to the DQSA. Table 5 shows the number of states that reported having laws, regulations, or policies specific to drug compounding, including pending or proposed laws, regulations, or policies, and those specific to nonpharmacist health care practitioners and FDA-registered outsourcing facilities.

Table 5: Laws, Regulations, or Policies Related to Drug Compounding, by Number of Reporting States, as of January 1, 2016

	Number of states with law, regulation, or policy (%)			
State law, regulation, or policy	**Yes**	**No**	**Don't know**	**No response**
Laws, regulations, or policies specific to the practice of drug compounding	48 (96)	2 (4)	0 (0)	0 (0)
Laws enacted, or regulations or policies adopted, related to drug compounding in response to the federal Drug Quality and Security Act (Pub. L. No. 113-54) enacted in November 2013	26 (52)	24 (48)	0 (0)	0 (0)
Additional legislation, regulations, or policies related to drug compounding under consideration	30 (60)	12 (24)	6 (12)	2 (4)
Laws, regulations, or policies specific to drug compounding by physicians or other nonpharmacist health care practitioners	9 (18)	23 (46)	17 (34)	1 (2)
Pending or proposed laws, regulations, or policies specific to drug compounding by physicians or other nonpharmacist health care practitioners	3 (6)	23 (46)	22 (44)	2 (4)
Laws, regulations, or policies specific to Food and Drug Administration (FDA) registered outsourcing facilities	17 (34)	27 (54)	4 (8)	2 (4)
Pending or proposed legislation specific to FDA-registered outsourcing facilities	13 (26)	28 (56)	7 (14)	2 (4)

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Note: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

[22]The board of pharmacy official in Pennsylvania said that while Pennsylvania did not have any laws specific to the practice of drug compounding at the time of our review, the state does have a provision in state law regarding pharmacy supplies and preparing prescriptions that their inspectors can use when they encounter pharmacies that compound drugs, and that their inspectors are trained in USP chapters 795 and 797 compounding standards.

In addition, respondents in 39 states reported that anticipatory compounding for both sterile and nonsterile compounded drugs is authorized or allowed in their state, and respondents in 27 states reported that compounding for office use is authorized or allowed in their state. However, respondents in 4 of the 27 states commented that only FDA-registered outsourcing facilities may compound drugs for office use and a respondent in 1 state reported that their state was working on regulations to prohibit this practice to align with federal restrictions on pharmacies under section 503A.[23] In our three selected states, compounding for office use is allowed in Texas, but not in North Carolina or Minnesota. The Texas board of pharmacy official said that the state enacted legislation to allow compounding for office use in 2005, but noted that the volume of office-use compounding in pharmacies appears to have dropped dramatically because outsourcing facilities registered with FDA are now providing this service. The North Carolina board of pharmacy official told us that North Carolina revised its laws regarding compounding for office use following enactment of the DQSA and this practice is no longer allowed in the state. This official said that there is no such thing as office-use compounding in North Carolina unless a facility is registered with FDA as an outsourcing facility. According to the Minnesota board of pharmacy official, compounding by licensed pharmacies for office use has not been allowed in the state for decades, and an exemption that had been provided for some large health care systems and specialty pharmacies to compound products to use within their system is no longer available.

State laws, regulations, and policies related to licensing for sterile drug compounding, labeling and testing of compounded drugs, compounding qualifications and standards, and reporting of compounded drug products

[23]Anticipatory compounding is the creation of a drug product prior to receipt of an individual patient prescription in anticipation of receiving prescriptions based on historical prescribing patterns. Drug compounding for office use is the compounding of a drug product, without an individual patient prescription, to be kept as stock in a doctor's office, hospital, or other health care facility. To qualify for exemption from the requirement to follow CGMP requirements and other FDCA provisions under section 503A of the FDCA, 503A compounders may only compound based on (1) the prescription order for an individual patient, or (2) in limited quantities before the receipt of a valid prescription order for such individual patient, and based on a history of valid prescription orders for the compounded drug product. 21 U.S.C. § 353a(a). Under section 503B of the FDCA, outsourcing facilities may compound drugs with or without a patient-specific prescription. 21 U.S.C. § 353b(d)(4)(C).

varied across states. For example, respondents in 12 states reported requiring a license or registration for sterile compounding facilities, and respondents in 24 states reported requiring labeling for compounded drugs, as of January 1, 2016. Table 6 provides a summary of select provisions related to drug compounding and the number of states that reported having each provision.

Table 6: Provisions Related to Drug Compounding, by Number of Reporting States, as of January 1, 2016

Provisions related to drug compounding	Number of states (%)
Licensing for sterile compounding	
License or registration for sterile compounding facilities	12 (24)
License or registration for pharmacists who prepare sterile compounded drugs	5 (10)
License or registration for physicians or other nonpharmacist health care practitioners who prepare sterile compounded drugs	3 (6)
Labeling and testing of compounded drugs	
Compounded drug products are required to have labeling that indicates that the drug is a compounded drug	24 (48)
Sterile compounded drugs are subject to random or routine sampling for potency, purity, and sterility	25 (50)
Compounding qualifications and standards	
Pharmacy staff are required to demonstrate competence in sterile compounding	33 (66)
Compliance with the U.S. Pharmacopeial Convention (USP) Chapter 797 Pharmaceutical Compounding-Sterile Preparations (in part or whole)	33 (66)
Sterile compounding continuing education for licensed pharmacists and/or pharmacy technician	12 (24)
State inspectors must have competence in sterile compounding	22 (44)
Reporting of compounded drugs	
Adverse drug events are reported to the state pharmacy board or other state entity, or FDA's MedWatch program[a]	19 (38)
Nonresident states report to resident state board of pharmacy on any actions taken against resident entities	28 (56)
Complaints filed by another state are reported to the state pharmacy board or other state entity	32 (64)

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

[a]MedWatch is the Food and Drug Administration's (FDA) adverse event reporting system.

Further, respondents in 40 states reported that they require FDA-registered outsourcing facilities that conduct business within their state to have a license in their state, and some states require more than one license type for FDA-registered outsourcing facilities. (See table 7.) For example, one state reported that an FDA-registered outsourcing facility is required to register with the state as a manufacturer, but if the facility is also providing compounded drugs for patient-specific prescriptions the facility must also register as a pharmacy.

Table 7: State Licensing Requirements for FDA-Registered Outsourcing Facilities, by Number of Reporting States

State licensing requirement	Number of states[a]
Pharmacy	20
Wholesale distributor	19
Manufacturer	10
Outsourcing facility (licensed or registered by the state)	12

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

In addition, one state reported requiring Food and Drug Administration (FDA) registered outsourcing facilities to be licensed as sterile compounding pharmacies.

[a]Total numbers exceed 40 because of states that require registration for more than one license type.

Some states also have different licensing categories for resident (in-state) and nonresident (out-of-state) FDA-registered outsourcing facilities, and oversight of these facilities varies by state. For example, in our three selected states:

- **Minnesota.** The Minnesota Board of Pharmacy has oversight responsibility for outsourcing facilities in Minnesota. The board of pharmacy official said that under Minnesota law, outsourcing facilities are considered to be a subtype of manufacturer and are required to follow CGMP requirements.[24] This law also specifies that no license shall be issued or renewed for an outsourcing facility unless the applicant provides proof of registration with FDA as an outsourcing facility, according to the official.
- **North Carolina.** The North Carolina Department of Agriculture and Consumer Services, Food and Drug Protection Division, has oversight responsibility for outsourcing facilities in North Carolina. According to an official from this department, a state statute specifically refers to outsourcing facilities and applies the same requirements applicable to conventional drug manufacturers to these facilities, including the requirement to register with the department.[25] As with conventional drug manufacturers, the department has oversight responsibility for

[24]Minn. Stat. § 151.252, subd. 1a.

[25]N.C. Gen. Stat. § 106-140.1.

the storage and distribution of outsourcing facilities' finished products.[26]

- **Texas.** The Texas Department of State Health Services, Drugs and Medical Devices Group, has oversight responsibility for outsourcing facilities in Texas. Officials from this department told us that in-state facilities are licensed as manufacturers of prescription drugs, and out-of-state facilities are licensed as prescription drug distributors. The officials said that Texas law does not specifically address outsourcing facilities; therefore, they regulate these entities as manufacturers and apply federal regulations and FDA guidelines and policies in their oversight of these entities, including inspecting them under CGMP requirements.

Few States Reported Having Laws or Policies Specific to Drug Compounding by Physicians and Other Nonpharmacist Health Care Practitioners

Respondents in less than 20 percent of states (9 states) reported having laws, regulations, or policies specific to compounding by physicians or other nonpharmacist health care practitioners (e.g., physician assistants), and these laws varied by state. For example, one state reported that its state statute requires pharmacy board licensure of all entities that compound drugs and possess compounded drugs, including physicians; and another state reported having a law that specifically allows a medical practitioner to compound drugs for patients under the practitioner's care.

Officials in one of our three selected states—Minnesota—reported having a law specific to compounding by physicians and other nonpharmacist health care practitioners. Officials in the two other states reported that they did not have any laws, regulations, or policies specific to such compounding.

- **Minnesota.** Minnesota's statute on compounding applies to both health care practitioners and pharmacies.[27] The Minnesota statute requires practitioners and pharmacists to comply with USP compounding standards, among other things. However, an official

[26]The North Carolina official reported that there were two outsourcing facilities in North Carolina. One of these facilities is a dual-purpose facility in that it is a compounding pharmacy (compounding drugs for specific patients in accordance with a prescription) and an outsourcing facility registered with FDA, and the other facility is also a dual-purpose facility licensed as a drug manufacturer and an outsourcing facility registered with FDA.

[27]Minn. Stat. § 151.253. subd. 2.

from the Minnesota Board of Pharmacy told us that the pharmacy board relies on the state's Board of Medical Practice to inform physicians that compounding by physicians should be compliant with the USP chapters related to nonsterile and sterile compounding (USP chapters 795 and 797, respectively) depending on what they are compounding. This official said that the board of pharmacy does not know which physicians may be compounding, and while the pharmacy board has the authority to inspect any place in the state in which drugs are held to be distributed, they need to give advance notice of inspection to physicians. An official from the Minnesota Board of Medical Practice said that the medical board has a complaint-driven process and that if there are allegations that a physician has violated medical or pharmacy statutes that regulate the practice of medicine, including compounding, the board has the authority to investigate.

- **North Carolina.** A state statute in North Carolina requires that a physician who dispenses prescription drugs, for a fee or other charge, register with the board of pharmacy and comply with relevant laws and regulations governing distribution of drugs that apply to pharmacists; however, this statute does not specifically address compounding by physicians.[28] According to the board of pharmacy official we interviewed, disciplinary authority over these physicians lies solely with the state's medical board. The North Carolina Medical Board official explained that the board has the authority to discipline a physician for violating any law involving the practice of medicine and that compounding drugs is included in the practice of medicine. This official further explained that the board's role in overseeing physicians has historically been complaint driven and the board had not had any complaints or issues brought to its attention related to compounding by physicians until a recent case referred to them by the board of pharmacy. This official said that the board is currently developing its role in overseeing compounding by physicians.
- **Texas.** The Texas medical board official told us that there was no specific mention of compounding by physicians in the Texas state statute. The official said, however, that if the medical board received a complaint that involved one of their licensees (i.e., practitioner) violating the state's drug compounding laws, then the board could take enforcement actions.

[28]N.C. Gen. Stat. § 90-85.21(b).

Respondents in 21 states reported that their office had heard concerns about the practice of compounding by physicians and other nonpharmacists. Some of the concerns respondents in these states reported were about a lack of regulation and oversight of compounding by physicians and other nonpharmacists, and whether physicians were complying with compounding standards, such as USP standards. Further, respondents in some states were unsure which entity, if any, in their state had oversight responsibility for compounding by physicians and other nonpharmacists. For example, respondents in 17 states reported that they did not know if their state had any laws, regulations, or policies specific to drug compounding by nonpharmacists. A respondent in one state commented that they do not believe that the medical, nursing, and naturopath practitioners are subject to any laws, regulations, or policies related to compounding.

Some of the stakeholder organizations we interviewed also expressed concerns about compounding by physicians and other nonpharmacists. Officials from one stakeholder organization said that drug compounding conducted in standalone physician practices does not generally fall under medical licensing requirements of state medical boards; therefore, there are gaps in oversight of compounding by physicians. Officials from another stakeholder organization told us that there are an increasing number of companies that are targeting physicians, offering to establish compounding labs within the physicians' offices. The officials said that the market has been responding to DQSA by targeting physicians because FDA's oversight of drug compounding has focused on pharmacists, and the market sees an opportunity for physicians to profit off of compounding rather than see the prescriptions they write leave their offices. An official from another stakeholder organization said that there is an enormous amount of compounding in physician offices, but few state boards of pharmacy have oversight over this practice. This official said that boards of pharmacy oversee pharmacists and pharmacies, but do not oversee compounding by physicians. According to this official, the state boards of pharmacy have tried to bring physician-compounded drugs under their oversight, but it has been difficult. Officials from one stakeholder organization, the Federation of State Medical Boards, told us that they conducted an informal review of state laws regarding compounding by physicians (i.e., state medical practice acts) and found that few states have laws specifically regulating compounding by physicians; however,

most medical boards consider compounding as part of the practice of medicine. The officials said that they plan to further study this issue to determine whether to develop guidelines for their members.[29] In addition, FDA officials told us that the agency has not taken a proactive role in compounding by physicians and there is not much oversight of physician compounding by state medical boards. FDA officials noted that they did inspect one physician who was compounding after receiving complaints, and that they planned to discuss oversight of physician compounding at FDA's intergovernmental meeting with state officials in September 2016.

Most States Reported Inspecting Resident Pharmacies and Can Take a Variety of Enforcement Actions to Enforce Drug Compounding Laws

To help ensure compliance with state laws, regulations, or policies related to drug compounding, respondents in most states reported inspecting resident pharmacies and relying on inspections by the home state of nonresident pharmacies. Specifically, respondents in 42 states reported inspecting all licensed resident pharmacies, respondents in 6 states reported inspecting some of these pharmacies, and respondents in 29 states reported relying on a home state's inspection report for nonresident pharmacy inspections.[30] Specific to entities that compound or distribute sterile compounded drugs, table 8 shows the number of states that

[29]Officials from the Federation of State Medical Boards told us that they introduced a draft position statement to their House of Delegates on the compounding of medications by physicians in April 2016; however, after receiving comments from stakeholder organizations, the officials said that their Committee on Ethics and Professionalism will continue to study the issue of compounding by physicians, and that they are in discussions with FDA and USP officials regarding this issue.

[30]For the 2 remaining states that did not report inspecting all or some licensed resident pharmacies, the respondent in 1 state reported that their state does not inspect resident pharmacies and the other state did not respond to this question. For the 21 remaining states that did not report relying on home state inspections for licensed nonresident pharmacies, respondents in 6 states reported inspecting some or all nonresident pharmacies, 14 states reported that their states do not inspect nonresident pharmacies, and 1 state did not respond to this question.

According to officials from the National Association of Boards of Pharmacy, in most cases, states do not have the capacity to inspect pharmacies in other states and, therefore, must rely on information from either the pharmacy's home state, a third party, or both in order to make informed licensing decisions. The officials said the association has been working to develop and implement an inspection blueprint to achieve consistency, quality, and reliability of inspections across states, so that a nonresident state can be comfortable accepting an inspection report from a home state that uses the blueprint.

reported conducting inspections for sterile compounding pharmacies, wholesale distributors, and outsourcing facilities.

Table 8: Number of States That Reported Inspecting Resident and Nonresident Sterile Compounding Pharmacies, Wholesale Distributors, and Outsourcing Facilities

	Number of states (%)					
Type of entity	Yes, all	Yes, some	No	State does not have this type of entity	Rely on home state inspection (nonresident only)	No response
Resident sterile compounding pharmacy[a]	36 (72)	3 (6)	2 (4)	8 (16)	N/A	1 (2)
Nonresident sterile compounding pharmacy[a]	5 (10)	3 (6)	11 (22)	5 (10)	25 (50)	1 (2)
Resident wholesale distributor	33 (66)	9 (18)	5 (10)	1 (2)	N/A	2 (4)
Nonresident wholesale distributor	1 (2)	2 (4)	19 (38)	0 (0)	26 (52)	2 (4)
Resident outsourcing facility	24 (48)	2 (4)	11 (22)	12 (24)	N/A	1 (2)
Nonresident outsourcing facility	3 (6)	2 (4)	17 (34)	8 (16)	19 (38)	1 (2)

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

[a]Twelve states reported having a separate state license category for resident sterile compounding pharmacies, and 12 states reported having a category for nonresident sterile compounding pharmacies; however, some states reported that they inspect pharmacies they know are compounding sterile drugs even if their state does not have a specific license category for these entities.

Types of state inspections include prelicensure, for cause (e.g., in response to a complaint), and recurring (e.g., every 1 to 2 years). Respondents in most states reported conducting these types of inspections for resident pharmacies, resident sterile compounding pharmacies, and resident wholesale distributors; however, few states reported conducting any of these types of inspections for nonresident entities. In addition, the number of full-time equivalent pharmacy inspectors authorized to inspect either resident or nonresident pharmacies, or both, ranged from zero to 138. A respondent in one state that did not have any pharmacy inspectors reported that the five pharmacy board members conducted these inspections.

Survey respondents also reported their states required certain qualifications for pharmacy inspectors. For example, most respondents reported that their state required inspectors to have a current pharmacist's license and almost half the states required inspectors to have practiced pharmacy for a minimum number of years. Specific to

inspections of compounding facilities, respondents in 21 states reported requiring inspectors to complete a specialized training program in sterile compounding, respondents in 15 states reported requiring inspectors to complete a specialized training program in nonsterile compounding, and respondents in 4 states reported requiring inspectors to have prior experience in compounding.

Time frames for recurring inspections of pharmacies and other drug compounders, as well as entities that distribute compounded drugs, vary by state, and respondents in some states reported challenges in meeting their inspection time frames. Respondents reported state inspection time frames ranging from at least once a year to every 5 years or more, and they also varied by type of entity being inspected. (See table 9.) Respondents in 21 states reported that they have challenges in meeting their state's required inspection time frames, citing reasons such as limited resources and the time required to conduct inspections. For example, a respondent in one state commented that there are over 1,000 sterile compounding pharmacies in their state that are supposed to be inspected each year, which is challenging for the 46 inspectors who conduct these inspections. A respondent in another state commented that they have a small staff responsible for inspections and investigations, so the priority goes to sterile compounding facilities.

Table 9: Frequency of Recurring Inspections, by the Number of States That Reported Conducting Them

	Number of states				
Type of entity inspected	**At least once a year**	**1 – up to 2 years**	**2 – up to 3 years**	**3 – up to 5 years**	**5 or more years**
Resident pharmacy	13	16	9	2	1
Nonresident pharmacy	0	2	0	0	0
Resident sterile compounding pharmacy[a]	21	11	4	2	0
Nonresident sterile compounding pharmacy[a]	1	3	0	0	0
Resident wholesale distributor	5	13	4	4	1
Nonresident wholesale distributor	0	1	0	0	0
Resident outsourcing facility	11	9	1	2	0
Nonresident outsourcing facility	1	2	0	0	0

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

[a]Twelve states reported having a separate state license category for resident sterile compounding pharmacies, and 12 states reported having a category for nonresident sterile compounding

pharmacies; however, some states reported that they inspect pharmacies they know are compounding sterile drugs even if their state does not have a specific license category for these entities.

To enforce drug compounding laws, regulations, or policies, respondents in most states reported they can take several types of actions against pharmacies or other compounding entities, including suspension and revocation of a license or registration, monetary fines, or a cease and desist order. For example, respondents in 45 states reported they can suspend a pharmacy or pharmacist's license and respondents in 41 states reported they can impose monetary fines. (See table 10.) Other types of actions that respondents reported included nondisciplinary administrative letters of warning, restricting a license (e.g., restricting a pharmacist from engaging in sterile compounding), and reprimands.

Table 10: Types of Enforcement Actions That Can Be Taken Against Licensed or Registered Pharmacists or Pharmacies, by the Number of States That Reported They May Take this Action

Type of enforcement action	Number of states
Suspension of pharmacist/pharmacy license	45
Voluntary relinquishment or surrender of pharmacist/pharmacy license	42
Probation of licensed pharmacist/pharmacy	42
Revocation of pharmacist/pharmacy license	41
Monetary fine	41
Cease and desist order	34
Prosecution under state or federal law	25
Mandatory recall of compounded drugs	19

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Note: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

While respondents in several states reported data on the number of actions taken against pharmacies for cases involving compounded drugs, respondents in some states reported that they do not track such data specific to cases involving compounded drugs. Of the respondents in the 41 states that reported they can impose a monetary fine, 13 states reported imposing monetary fines on pharmacies or pharmacists for cases involving compounded drugs in 2014, and 12 states reported taking this action in 2015. The number of pharmacies or pharmacists that states reported receiving these fines in 2015 ranged from 1 pharmacy or pharmacist in 1 state to 73 in another state. In addition, respondents in 8 states reported suspending pharmacy or pharmacist licenses in 2014 and

respondents in 6 states reported taking this action in 2015. Of the respondents in the 19 states that reported they can conduct a mandatory recall of compounded drugs, 2 states reported taking this action in 2014 and 3 states reported doing so in 2015. Respondents in 4 states reported revoking 1 or 2 pharmacy or pharmacist licenses in 2015 for cases involving compounded drugs.

Most States Are Satisfied With Their Communication with FDA and Other States, although Some States Reported Challenges

Most states reported overall satisfaction with their communication with FDA on compounding issues through events such as FDA-sponsored activities, but some states reported challenges with this communication. Similarly, most states reported overall satisfaction with communication among states at conferences and meetings, but some states noted challenges.

About Three Quarters of States Reported Participating in FDA-Sponsored Activities and Obtaining FDA Drug Compounding Information; Some States Reported Challenges with This Communication

FDA has communicated with states on compounding issues in a variety of ways, including FDA-sponsored activities, such as intergovernmental meetings; most states reported this communication was helpful. In 2014 and 2015, FDA held three intergovernmental working meetings on pharmacy compounding with pharmacy board representatives from states and U.S. territories.[31] Survey respondents in about three quarters of the states reported participating in FDA's intergovernmental meetings on drug compounding, and most participating states reported these activities were very or moderately helpful; however, a number of participating states reported that the activities were slightly or not at all helpful. For example, respondents in 41 states reported participating in FDA's March 2014 Intergovernmental Working Meeting on Pharmacy Compounding, and of those states that reported participating in this meeting, respondents in 33 states, or about 80 percent, reported that the meeting was very or moderately helpful. However, respondents in 4 states that reported participating in the March 2014 meeting reported that the meeting was

[31]FDA held its fourth intergovernmental working meeting on pharmacy compounding since enactment of the DQSA on September 20 and 21, 2016.

slightly or not at all helpful. See table 11 for the number of states that reported participating in FDA-sponsored activities and how the participating states rated the helpfulness of the activities.

Table 11: States That Reported Participating in FDA-Sponsored Activities Related to Drug Compounding and How These States Rated the Helpfulness of Each Activity

	Number of states that reported participating in activity (%)				How states that reported participating in FDA-sponsored activities rated the helpfulness of each activity			
Food and Drug Administration (FDA) sponsored activity	Yes	No	Don't know	No response	Very or moderately helpful	Slightly or not at all helpful	Don't know	No response
FDA's March 2014 Intergovernmental Working Meeting on Pharmacy Compounding	41 (82)	2 (4)	4 (8)	3 (6)	33	4	2	2
FDA's March 2015 Intergovernmental Working Meeting on Pharmacy Compounding	37 (74)	7 (14)	4 (8)	2 (4)	28	5	3	1
FDA's November 2015 Intergovernmental Working Meeting on Pharmacy Compounding	35 (70)	11 (22)	1 (2)	3 (6)	25	6	2	2
FDA's Pharmacy Compounding Advisory Committee meeting, February 2015[a]	8 (16)	31 (62)	9 (18)	2 (4)	6	2	0	0
FDA's Pharmacy Compounding Advisory Committee meeting, June 2015[a]	7 (14)	34 (68)	5 (10)	4 (8)	5	2	0	0

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

[a]The Drug Quality and Security Act, enacted in November 2013, required FDA to convene and consult with a Pharmacy Compounding Advisory Committee before issuing certain regulations.

Respondents from most states reported obtaining compounding-related information from FDA's website, and in general, states found this information helpful. For example, respondents in 38 states reported obtaining a list of FDA-registered outsourcing facilities from FDA's website, and 32 of them found the information very or moderately helpful. See table 12 for the number of states that reported obtaining information related to drug compounding from FDA's website and how these states rated the helpfulness of the information.

Table 12: The Number of States That Reported Obtaining Information Related to Drug Compounding from FDA's Website and How These States Rated the Helpfulness of This Information

Information on the Food and Drug Administration's (FDA) website	Number of states that reported obtaining the information (%)			How states that reported obtaining the information rated the helpfulness of the information			
	Yes	No	No response	Very or moderately helpful	Slightly or not at all helpful	Don't know	No response
List of FDA-registered outsourcing facilities	38 (76)	10 (20)	2 (4)	32	3	0	3
Names of compounding pharmacies that were inspected by FDA	33 (66)	15 (30)	2 (4)	29	3	0	1
FDA Form 483 inspection observation reports to determine violations found during inspections of compounding pharmacies	35 (70)	13 (26)	2 (4)	25	7	1	2
FDA Form 483 inspection observation reports to determine violations found during inspections of FDA-registered outsourcing facilities	33 (66)	15 (30)	2 (4)	23	6	1	3
FDA warning letters issued to compounding pharmacies	35 (70)	13 (26)	2 (4)	27	6	1	1
FDA warning letters issued to FDA-registered outsourcing facilities	32 (64)	16 (32)	2 (4)	26	4	1	1
Information on recalls of compounded drugs	36 (72)	12 (24)	2 (4)	30	3	1	2

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

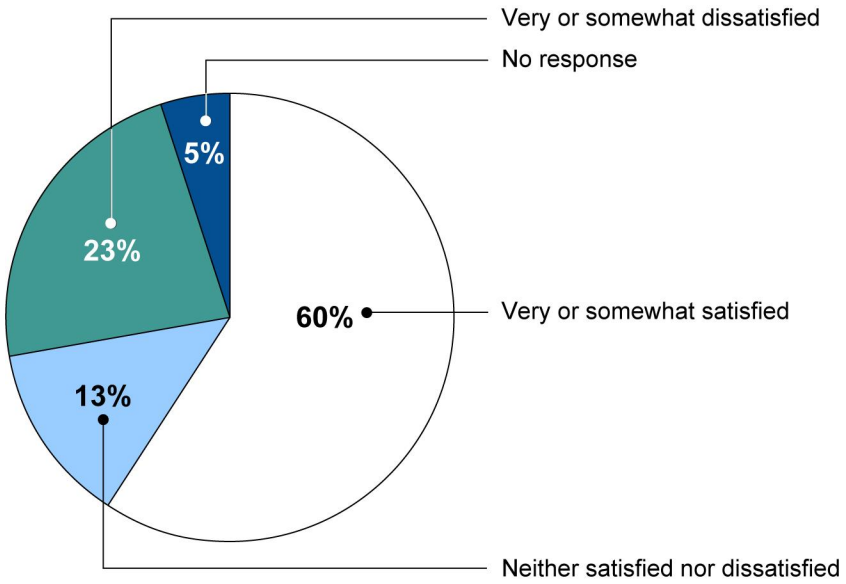
Note: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

Of the respondents in the 40 states that reported having had communication with FDA regarding drug compounding issues, 24 states (60 percent) reported that, overall, they were very or somewhat satisfied with this communication; however, 9 states (23 percent) reported they were very or somewhat dissatisfied. (See fig. 1.) The respondent in one state that reported being satisfied with their communication with FDA said "It has been very helpful to have ongoing meetings and discussion with FDA at FDA-sponsored events and other meetings. The emphasis on state communication is noted and appreciated." However, the respondent in another state that indicated dissatisfaction with their communication with FDA commented that "there seems to be no real progress in

providing guidance as to what regulatory approaches FDA intends to take—it seems like FDA is burdened by red tape that prevents it from sharing information with the states on common issues."

Figure 1: Percentage of States Reporting each Level of Satisfaction with Food and Drug Administration (FDA) Communication Regarding Drug Compounding

Forty states that reported having had communication or interactions with FDA related to drug compounding issues were asked about their overall satisfaction with that communication or interaction.



Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

Percentages exceed 100 percent because of rounding.

Respondents in 25 states reported that they have not experienced specific challenges in their communication or interactions with FDA related to drug compounding issues, but respondents in 15 states reported experiencing one or more communication challenge with FDA. Fourteen of them reported that getting FDA to respond to their requests for information was very or moderately challenging; and 10 of them reported that getting FDA to provide responses to their questions related to oversight of drug compounding was very or moderately challenging. Finally, respondents in several states elaborated on their states' communication or interactions with FDA. For example, one respondent reported that "it has taken years for the FDA to respond or even acknowledge the Board's communication in some instances. Timeliness

is a significant issue." Another respondent reported that when they work with FDA, FDA requests a variety of information from the board, but will not provide any information to the board. See table 13 for how 15 states—the states that reported experiencing one or more communication challenges with FDA—rated these challenges.

Table 13: States Reporting Challenges in Communication or Other Interactions with FDA

Types of communication or interactions with the Food and Drug Administration (FDA) that posed a challenge	Significance of challenges in communication or other interactions with FDA reported by 15 states reporting challenges				
	Number of states				
	Very challenging	Moderately challenging	Slightly challenging	Not at all challenging	Not applicable
Getting FDA to respond to our requests for information	7	7	1	0	0
Scheduling an individual meeting with FDA	2	2	5	3	3
Getting FDA to provide responses to our questions related to oversight of drug compounding	4	6	3	0	2
Getting notification of pharmacy inspections conducted by FDA in our state	2	4	2	6	1
Getting complete information from FDA in Form 483 inspection observation reports on pharmacy inspections conducted by FDA in our state	5	2	3	3	2
Getting FDA approval of our requests for joint inspections of licensed or registered pharmacies in our state[a]	2	1	3	1	7
Getting notification from FDA when FDA determines a licensed or registered pharmacy in our state is acting contrary to section 503A of the Federal Food, Drug, and Cosmetic Act	5	3	0	3	4
Getting notification from FDA of FDA enforcement actions taken against licensed or registered pharmacies in our state	3	5	0	3	4

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

[a]One of the 15 states did not indicate a significance of the challenge related to this type of communication or interaction with FDA.

FDA officials noted that federal law prohibits FDA from sharing certain nonpublic information with state officials that have not provided

confidentiality commitments to FDA. According to FDA officials, the agency has encouraged and worked with states and individual state officials to provide such commitments through FDA commissioning or information sharing agreements.[32] Survey respondents in 27 states reported having commissioned officers with FDA; 16 of them reported that having commissioned officers for sharing information and conducting activities related to drug compounding was very or somewhat effective, and 5 of them reported having commissioned officers was very or somewhat ineffective.[33] A respondent in one state reported that having commissioned officers "has expedited the sharing of information," while a respondent in another state reported "the inability to share information with other staff, the board, or to use the information obtained through commissioner status in disciplinary actions against the subject licensee makes this process ineffective and inefficient." In addition, 11 states reported having an information sharing agreement with FDA; 8 of them reported this agreement was very or somewhat effective for sharing information related to drug compounding, and 2 of them reported the agreement was neither effective nor ineffective.[34] A respondent in one state reported "information sharing [with FDA] has improved greatly in the past two years." However, a respondent in another state reported "the process still feels like the state needs to pry information from the FDA."

We also asked the stakeholder organizations about FDA's communication with the states related to drug compounding. Seven of the 25 stakeholder organizations we interviewed said that, overall, communication between the states and FDA has improved since the DQSA was enacted;

[32]A state official may be commissioned as an officer of FDA and, by virtue of this status, be eligible to receive FDA-owned nonpublic information. 21 U.S.C. § 372. FDA may also share certain nonpublic information, such as deliberative and confidential commercial information, with state officials under a written confidentiality agreement. 21 C.F.R. § 20.88. For example, FDA created a 5-year, single signature "Long-Term Drug Compounding Information Sharing Agreement" to improve communications and facilitate oversight of compounding pharmacies.

[33]For the six remaining states, respondents in five states reported that they did not know how effective having commissioned officers was for sharing information related to drug compounding and one state did not provide a response.

[34]The remaining state did not respond to the effectiveness of the information sharing agreement.

however, 2 stakeholder organizations commented that FDA only has one-way communication with states.

Communication among States Occurs through Several Venues and Activities; Most States are Satisfied with this Communication, but Some Reported Challenges

Respondents in 42 states reported communicating with other states regarding issues related to drug compounding using venues such as national association meetings, e-mails, phone calls, and informal networking at FDA-sponsored events. Respondents in 35 states reported that they were very or somewhat satisfied with their communication and interactions with other state pharmacy regulatory bodies related to drug compounding issues. See table 14 for the number of states reporting having various types of communications or interactions with other state regulatory bodies, and how these states rated the helpfulness of the communication or interaction.

Table 14: Helpfulness of Communication and Interactions with Other State Pharmacy Regulatory Bodies, by States That Reported Having Communication and Interactions

	Number of states			
	States reporting having communication or interaction	Helpfulness of communication or interaction		
Type of communication or interaction with other state pharmacy regulatory bodies		Very or moderately helpful	Slightly or not at all helpful	Don't know
National associations (e.g., National Association of Boards of Pharmacy conferences, annual national association meetings)	39[a]	34	3	1
Regional associations (e.g., conferences or regional meetings)	26	22	4	0
State-to-state direct communication (e.g., in-person meetings, phone calls and/or emails with other state boards of pharmacy)	34	33	1	0
Conduct joint inspections with other state boards of pharmacy or other state pharmacy regulatory bodies	9	8	1	0
Informal networking with other states that takes place at events sponsored by the Food and Drug Administration or industry	33	32	1	0
Other types of interactions (e.g., meetings with state boards of pharmacy and state associations)	6	6	0	0

Source: GAO survey of state pharmacy regulatory bodies. | GAO-17-64

Notes: GAO surveyed the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, and all but 4 completed the survey.

[a]One of the 39 states did not indicate a level of helpfulness of national association meetings.

Respondents in 35 states reported that they had not experienced challenges regarding their communication or interactions with other state pharmacy regulatory bodies related to drug compounding issues, but respondents in 5 states did report challenges. One of the 5 that reported challenges commented that some states do not return phone calls, and other states have little or no resources. Another respondent that reported challenges commented that there needs to be a single national model regarding the regulation and licensure of compounding pharmacies.

FDA Has Taken Steps to Implement Its Drug Compounding Responsibilities, but States and Stakeholder Organizations have Cited Challenges and Concerns

FDA has taken steps to implement its drug compounding responsibilities since enactment of the DQSA, but states and stakeholder organizations have cited a number of challenges and concerns. FDA has issued numerous guidance documents related to drug compounding, and conducted more than 300 inspections of drug compounders. However, some stakeholder organizations said the amount of time it takes FDA to finalize guidance and other key documents is challenging. States and stakeholder organizations also cited concerns regarding FDA's implementation of its drug compounding responsibilities.

FDA Has Released Final and Draft Documents Related to Drug Compounding, and Conducted More than 300 Inspections of Drug Compounders

FDA has issued numerous documents related to compounding since the DQSA was enacted; most of these are draft documents. FDA has released final guidance on adverse event reporting requirements, the process and fees related to registering with FDA as an outsourcing facility, and pharmacy compounding under section 503A, among others. The remaining guidance and other documents that are still in draft include documents that, according to many stakeholder organizations we interviewed, are key to FDA's implementation of its drug compounding responsibilities. See table 15 for final guidance, draft guidance, and other draft documents issued by FDA.

Table 15: Final and Draft Documents Related to FDA's Drug Compounding Regulatory Responsibilities

Date issued	Type	Title
Documents issued in final		
11/24/2014	Final guidance	Fees for Human Drug Compounding Outsourcing Facilities Under Sections 503B and 744K of the FD&C Act[a]
11/24/2014	Final guidance	Registration of Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act[a]
8/12/2015	Final guidance	Guidance For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
10/8/2015	Final guidance	Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
7/2/2014 (amended 10/26/2015 and 6/9/2016)	Final guidance	Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act
6/9/2016	Final guidance	Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act
6/9/2016	Final guidance	Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act
10/7/2016	Final rule	Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness
Documents issued in draft		
7/2/2014	Draft guidance	Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act[a]
11/24/2014	Draft guidance	Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act
2/13/2015	Draft guidance	Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities
2/13/2015	Draft guidance	Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application
2/13/2015	Draft memorandum of understanding[b]	Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State of [insert STATE] and the U.S. Food and Drug Administration
4/15/2016	Draft guidance	Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act
4/15/2016	Draft guidance	Hospital and Health System Compounding Under the Federal Food, Drug, and Cosmetic Act
4/15/2016	Draft guidance	Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act
7/7/2016	Draft guidance	Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act
7/7/2016	Draft guidance	Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Date issued	Type	Title
8/3/2016	Draft guidance	Insanitary Conditions at Compounding Facilities
10/18/2016	Proposed rule	Amendments to the Regulation Regarding the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness

Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-17-64

[a]The FD&C Act is an alternative abbreviation for the Federal Food, Drug, and Cosmetic Act.

[b]Under section 503A, FDA is required to develop, in consultation with the National Association of Boards of Pharmacy, a standard memorandum of understanding between states and FDA that addresses distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a state agency of complaints relating to drug products compounded in that state that are distributed outside the state.

According to our review of FDA data, FDA has also inspected drug compounders, including outsourcing facilities, and issued FDA form 483 inspection observation reports. FDA has also taken action, including issuing warning letters, when issues have been identified in these inspections. From May 2012 through April 22, 2016, FDA completed 265 inspections of 503A compounders and other drug compounders that were not outsourcing facilities. As of April 22, 2016, FDA had completed 75 inspections of outsourcing facilities. These 75 inspections were at 59 of the 91 facilities that had registered with FDA as an outsourcing facility. FDA officials noted that many of the entities that registered as outsourcing facilities withdrew their outsourcing facility registration submission before the agency scheduled an inspection, and others were not yet operating when the agency attempted to inspect them.

In general, FDA conducts three types of inspections: for-cause, follow-up, and surveillance. See table 16 for a description of FDA inspection types and the number of each type of inspection conducted by FDA for drug compounders as of April 22, 2016.

Table 16: Types of Food and Drug Administration (FDA) Inspections, and the Number of Inspections of Drug Compounders

Inspection type	Description	FDA inspections of 503A compounders (from May 2012 through April 22, 2016)[a]	FDA inspections of 503B outsourcing facilities (through April 22, 2016)[b]
For cause	FDA conducts for-cause inspections usually in response to a complaint, such as a report of a serious adverse event or product quality problem (e.g., contamination).	121	6
Follow-up	FDA conducts inspections to follow up on earlier inspection findings and/or FDA regulatory actions. For example, if FDA inspected the drug compounder in the past and found concerning practices or if FDA took regulatory action, such as issuing a warning letter, FDA conducts a follow-up inspection to check whether the drug compounder has implemented adequate corrective actions.	40	15
Surveillance	FDA conducts surveillance inspections of some drug compounders that are not outsourcing facilities, including 503A compounders. These inspections are not in response to an immediate adverse event or complaint, but instead are meant to check on drug compounders of which FDA is aware (e.g., because of prior inspections or complaints). FDA is required to inspect outsourcing facilities on a risk-based schedule. According to agency officials, the agency's goal is to inspect outsourcing facilities within 2 months of their initial registration with FDA if they had not been recently inspected prior to registration, and then every 12-18 months thereafter.	104	54
	Total	**265**	**75**

Source: GAO analysis of FDA information. | GAO-17-64

[a]This includes inspections of 503A compounders and other drug compounders that are not outsourcing facilities. The 503A compounders are individuals or entities that are not outsourcing facilities that qualify for the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA), including pharmacies, physicians, and federal facilities. Drug compounders that do not qualify for the exemptions under section 503A, and are not outsourcing facilities under section 503B, are regulated as conventional manufacturers and are subject to the provisions of the FDCA applicable to such manufacturers.

[b]The Drug Quality and Security Act, enacted in November 2013, created the category of outsourcing facility, and FDA conducted its first inspection of an outsourcing facility on March 5, 2014.

According to agency officials, FDA's Center for Drug Evaluation and Research issues all inspection assignments for 503A compounders and outsourcing facilities. FDA officials told us that, in an effort to focus the

agency's resources efficiently, the center and the agency's Office of Regulatory Affairs approach the coordination and scheduling of drug-compounding-related inspection assignments from a national perspective.[35] Unlike outsourcing facilities or conventional manufacturers, 503A compounders are not required to register with FDA. As such, FDA is only aware of a small percentage of the thousands of pharmacies that compound drugs, and FDA does not inspect all 503A compounders, according to FDA officials.[36] For outsourcing facilities, which register with FDA, the agency is required to inspect them on a risk-based schedule.[37] As of May 23, 2016, 91 facilities had registered with FDA as outsourcing facilities at some point in time, and as of July 2016, FDA had inspected 46 of the 60 establishments with active outsourcing facility registrations at least once.[38]

According to agency officials, FDA's risk models—which are used to determine which facilities to inspect—use information from a number of sources, including FDA's Field Accomplishment and Compliance Tracking System. However, as we reported in 2013, this database does not consistently indicate the final inspection classification—that is, it does not always include accurate information about whether the agency's final determination was that an official action was indicated, voluntary action was indicated, or if no action was indicated from the results of the

[35]According to the officials, certain geographic areas seem to have a higher concentration of drug compounders that the agency has reason to inspect. Therefore, the officials said the center works closely with FDA's Office of Regulatory Affairs to assist FDA district offices that may become overwhelmed with the volume of compounding inspections. For example, FDA may order an inspection of a pharmacy in one district, but assign it to investigators from another district that has a lower inspection workload at that time.

[36]According to FDA officials, FDA uses a risk-based model, using factors such as prior regulatory actions, recall history, adverse event history, the history of complaints, and findings from prior inspections, to prioritize and make inspection assignments for 503A compounders and other drug compounders that are not outsourcing facilities.

[37]See 21 U.S.C. § 353b(b)(4).

[38]According to agency officials, FDA's goal is to conduct the initial inspections of outsourcing facilities within 2 months of the facility's registration, and to conduct surveillance inspections on each outsourcing facility every 12 to 18 months thereafter. Agency officials reported that in some cases, a facility may have registered as an outsourcing facility before the facility was operational; in these circumstances FDA would wait to inspect the facility until it is operational.

inspection.[39] We recommended that FDA address this shortcoming by taking steps to consistently collect reliable and timely information in FDA's databases on inspections and enforcement actions associated with compounded drugs; however, as of June 2016, FDA officials reported the agency's database did not consistently include final inspection classifications. According to FDA officials, the agency's database includes recommendations from the district office, which may differ from the final inspection classifications after the case has undergone further review by officials in the Center for Drug Evaluation and Research and the Office of Regulatory Affairs. FDA officials told us that the agency took steps in June 2016 to make sure the final inspection classifications in its database are accurate by (1) including a section on data entry—including updating the inspection classification in the database—in a June 2016 training on compounding for center and Office of Regulatory Affairs staff, and (2) discussing the inspection classification during the joint assessment call for compounding inspections in order to decide on a final inspection classification and to make sure this classification is updated in the database. The officials said that FDA plans to update the final classifications for inspections FDA has already conducted and for all inspections moving forward.[40]

According to agency officials, FDA invites the relevant state regulatory authority (generally the state board of pharmacy, state department of health, or both) to accompany FDA on inspections of drug compounders. During the inspection, FDA investigators collect evidence relating to

[39]See GAO-13-702. FDA classifies an inspection as "official action indicated" if objectionable conditions were found that warrant regulatory action by the agency. A classification of "voluntary action indicated" means that objectionable conditions that do not meet the threshold for regulatory action were identified and any corrective actions are left to the establishment to take voluntarily. A classification of "no action indicated" means that no objectionable conditions or practices were found during the inspection (i.e., conditions or practices that violate CGMP requirements), or if the significance of the documented objectionable conditions found does not justify further FDA action.

[40]For each inspection of a drug compounder, FDA conducts a joint assessment call involving officials from the Center for Drug Evaluation and Research and Office of Regulatory Affairs to conduct a more formal evaluation of the inspection results, including any violations, according to agency officials. At the conclusion of this call, the officials produce a document of findings and a recommended action with respect to that case. Recommended actions could include issuing a warning letter, pursuing an injunction, or sending a state referral letter. FDA could also recommend closing the case with no further actions as a result of the joint assessment call.

whether the drug compounder meets certain conditions of sections 503A or 503B, as applicable, and to conditions and practices that, if deficient, raise safety concerns for public health. The inspections typically focus on identifying any insanitary conditions that could cause a drug product to be contaminated with filth or rendered injurious to health in violation of the FDCA, and review practices that, if deficient, could lead to potency problems or labeling mix ups.[41]

From May 11, 2012, through April 22, 2016, FDA conducted 265 inspections of 210 different establishments of drug compounders that are not outsourcing facilities, including 503A compounders. As a result of these inspections, the agency issued 228 FDA form 483 inspection observation reports (finding problems such as dead insects in ceilings and other insanitary conditions), and has taken a number of actions.[42] (See table 17.)

[41]See 21 U.S.C. § 351(a)(2)(A).

[42]An FDA form 483 inspection observation report is issued to firm management at the conclusion of an inspection when FDA investigators have observed conditions that, in their judgment, may constitute violations of the FDCA and related acts.

While FDA provided data on inspections of 503A compounders and other drug compounders that are not outsourcing facilities from May 2012 through April 22, 2016, the agency provided data on the actions taken related to these inspections through June 28, 2016.

Table 17: The Number and Type of Actions Taken from May 2012 to June 28, 2016 Related to Food and Drug Administration (FDA) Inspections of Drug Compounders That are Not Outsourcing Facilities

Action	Number
Warning letter (to notify the compounder of significant violations of FDA regulations)	81[a]
Voluntary recall	72[b]
State referral letter (refers inspection findings to the applicable state regulatory agency)	31
Regulatory meeting (requested by FDA management to inform responsible individuals or firms about one or more practices, products, or other activities considered to be in violation of the law, and to discuss violations that would not be handled by other means)	1

Source: GAO analysis of FDA data. | GAO-17-64

Notes: This table includes actions related to inspections of 503A compounders and other drug compounders that are not outsourcing facilities. The 503A compounders are individuals or entities that are not outsourcing facilities that qualify for the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA), including pharmacies, physicians, and federal facilities. Drug compounders that do not qualify for the exemptions under section 503A, and are not outsourcing facilities under section 503B, are regulated as conventional manufacturers and are subject to the provisions of the FDCA applicable to such manufacturers.

The actions are related to inspections conducted from May 2012 through April 22, 2016.

In addition, the agency sought and obtained two warrants to inspect pharmacies that refused inspection during this time period and obtained nine injunctions against drug compounders that were not outsourcing facilities. FDA also took criminal enforcement actions against three drug compounders that were not outsourcing facilities related to inspections during this time period.

[a]This number represents the number of drug compounders that are not outsourcing facilities that received warning letters; a drug compounder may have had more than one inspection associated with a warning letter.

[b]In addition, two inspections resulted in FDA requests for recalls but no recalls occurred.

As of April 2016, FDA had conducted 75 inspections of 59 different outsourcing facilities. Actions related to its inspections of outsourcing facilities included 24 FDA warning letters and 15 voluntary recalls.[43] (See table 18.)

[43]While FDA provided data on inspections of outsourcing facilities from March 5, 2014, through April 22, 2016, the agency provided data on the actions taken related to these inspections through June 28, 2016.

Table 18: The Number and Type of Actions Taken from March 5, 2014, to June 28, 2016 Related to Food and Drug Administration (FDA) Inspections of Outsourcing Facilities

Action	Number
Warning letter (to notify an outsourcing facility of significant violations of FDA regulations)	24[a]
Voluntary recall	15
Untitled letter (to notify an outsourcing facility of violations that do not meet the threshold of regulatory significance of a warning letter)	1

Source: GAO analysis of FDA data. | GAO-17-64

Notes: The Drug Quality and Security Act, enacted in November 2013, created the category of outsourcing facility, and FDA conducted its first inspection of an outsourcing facility on March 5, 2014.

The actions are related to inspections conducted from March 5, 2014, through April 22, 2016.

In addition, the agency also obtained two injunctions against outsourcing facilities during this time period.

[a]This number represents the number of outsourcing facilities that received warning letters; an outsourcing facility may have had more than one inspection associated with a warning letter.

Some Stakeholder Organizations said the Amount of Time it Takes FDA to Finalize Draft Documents Related to Drug Compounding is Challenging

Officials from 6 of the 25 stakeholder organizations we interviewed said the amount of time it takes FDA to finalize guidance and other relevant documents, including the list of drugs that are difficult to compound, is challenging. For example, officials from one of these stakeholder organizations told us that, as a result, they were uncertain regarding how to move forward under the DQSA; they did not know how to advise their members without final guidance from FDA regarding the list of drugs that are difficult to compound.

In addition, FDA has not finalized the standard memorandum of understanding (MOU) under section 503A between FDA and states that choose to sign it. Under section 503A, unless a drug is compounded in a state that has entered into an MOU with FDA, a pharmacist, pharmacy, or physician cannot distribute, or cause to be distributed, compounded drug products outside the state in which they are compounded in quantities that exceed 5 percent of the total prescription orders dispensed or distributed by that pharmacy or physician. These restrictions and the terms of the MOU will apply, once the standard MOU is finalized and made available to the states for their consideration and signature, to drugs compounded under section 503A, and will not apply to drugs compounded by outsourcing facilities. The law requires the standard MOU, which FDA is to develop in consultation with the National Association of Boards of Pharmacy, to address the interstate distribution of inordinate amounts of compounded drug products and to provide for appropriate investigation by a state of complaints related to compounded

drug products distributed outside of the state.[44] Officials from two stakeholder organizations we talked to expressed concern regarding the time it is taking FDA to finalize the standard MOU. Specifically, they are concerned with the potential implications that the MOU may have on how they do business.

In particular, the draft MOU that FDA published for comment in February 2015, would restrict interstate distribution of compounded products under section 503A to less than 30 percent of the number of compounded and noncompounded drug products that a pharmacy, pharmacist, or physician in a state that has entered into the MOU distributes or dispenses both intrastate and interstate in a calendar month. Pharmacists, pharmacies, and physicians in states that have not entered into the MOU would be limited to distributing compounded drug products in quantities that do not exceed 5 percent of all prescription orders they dispense or distribute.[45]

Officials from five stakeholder organizations that we talked to said they were concerned that, in the draft MOU, FDA's proposed definition of distribution includes dispensing. Representatives from one pharmacist stakeholder organization stated that, if the MOU defines distribution interchangeably with dispensing, compounded drugs dispensed will be included in the 30 percent calculation for interstate distribution of compounded drugs. As a result, they are concerned that pharmacies that regularly dispense compounded drugs across state lines, such as pharmacies in the metropolitan Washington D.C. area, where the borders of the District of Columbia, Maryland, and Virginia are in close proximity, will be limited in the number of compounded drugs they can dispense to patients, even though some of these patients may only live a short distance from the pharmacy.[46]

[44]21 U.S.C. § 353a(b)(3)(B).

[45]Food and Drug Administration, *Addressing Certain Distributions of Compounded Human Drug Products Between the State of [insert STATE] and the Food and Drug Administration*, Draft Memorandum of Understanding, 80 Fed. Reg. 8874 (Feb. 19, 2015).

[46]The draft MOU includes a statement that FDA does not intend to include "prescriptions dispensed to a patient (or patient's agent), if the patient (or patient's agent) to whom the drug is dispensed carries the drug across State lines after it has been dispensed to the patients (or patient's agent) at the facility in which the drug was compounded" in the percentage of compounded drug products that a drug compounder may distribute interstate.

FDA officials cited a number of reasons for the time it has taken the agency to finalize the agency's draft drug compounding documents, including the time and steps required to solicit and evaluate comments and issue guidance. For example, FDA officials attributed the time it has taken to finalize the draft MOU and other documents to a number of factors, including the time needed to review public comments and to conduct public meetings with state boards of pharmacy; FDA has received over 3,000 comments on the agency's draft MOU alone, many of which raise complex policy issues that need to be resolved, according to agency officials. In addition, according to the officials, these documents must go through FDA's internal clearance process along with numerous other requirements before being finalized.

States and Stakeholder Organizations Cited Concerns Regarding FDA's Implementation of Its Drug Compounding Responsibilities

States and stakeholder organizations reported a number of concerns related to FDA's implementation of its drug compounding responsibilities. These concerns included the availability of compounded drugs for use in physicians' offices, a potential loss in patient access to needed medications, and conflicting federal and state inspection protocols.

In response to our survey of state pharmacy regulatory bodies, respondents from 30 states reported that they had heard concerns that FDA's implementation of DQSA would affect the availability of compounded drugs for use in physicians' offices, generally referred to as office-use compounding. FDA's April 15, 2016, draft guidance on the prescription requirement for drugs compounded under section 503A states that the agency interprets section 503A to require a valid prescription for an individual patient before a pharmacy may provide a compounded drug to a provider.[47] Therefore, the draft guidance indicates that compounding of a drug product to be kept as stock in a doctor's office, hospital, or other health care facilities without an individual patient prescription is not permitted by any pharmacy that is not an outsourcing facility. Officials from some of the stakeholder organizations we talked to have raised concerns that FDA's draft guidance is inconsistent with laws

[47]Department of Health and Human Services, Food and Drug Administration, *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act, Guidance for Industry, Draft Guidance*, (Silver Spring, Md.: April 2016). See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM496286.pdf, accessed April 18, 2016.

in states that allow compounding for office use, and respondents in 27 states reported that their state laws currently allow office-use compounding.[48]

FDA officials noted that the agency's policies with respect to the prescription requirement in section 503A are intended to protect patients from poor quality compounded drugs that could cause serious harm while preserving access to drugs compounded for office-use for patients who need them. They stated that the prescription requirement in section 503A is critical to differentiate compounding by pharmacies and physicians under section 503A from conventional manufacturing and compounding by outsourcing facilities, which are subject to routine FDA oversight. FDA officials also said that stakeholders should advise the agency if instances arise in which a health care facility that orders compounded drugs for office use to meet patients' medical needs is unable to obtain these drugs from outsourcing facilities.

Respondents in 23 states reported concerns about access to certain compounded drugs for patients with a medical need for these drugs. For example, for compounded drugs for which there is not a great demand, there is concern that outsourcing facilities would choose not to compound these drugs. Therefore, according to these respondents, there is a concern that if 503A compounders are not allowed to compound these drugs for office use, patients could lose access to needed medications.

Some states and stakeholder organizations reported differences between the protocols that some states and FDA use when inspecting pharmacies engaged in drug compounding that are not outsourcing facilities. Specifically, officials in the states noted that their states inspect pharmacies to assess their compliance with state pharmacy practice rules, which are often based on the standards in USP chapters 795 (nonsterile compounding) and 797 (sterile compounding). These officials said that although pharmacies meeting the requirements of section 503A are exempt from FDA's CGMP requirements, FDA's publicly available form 483 inspection observation reports have included observations related to CGMP requirements, even for those 503A compounders. FDA

[48]Respondents in 4 of the 27 states commented that only outsourcing facilities registered with FDA may compound drugs for office use.

officials indicated they were aware of concerns about this practice, and on July 13, 2016, FDA announced a change in the agency's procedures that took effect on August 1, 2016. Under the new procedures, FDA investigators first make a preliminary assessment of whether a compounder's drugs are exempt from CGMP requirements under section 503A. If the preliminary assessment is that the compounder's drugs are exempt, the investigator will not issue an inspection observation report showing observations solely related to noncompliance with CGMP requirements. Instead, the FDA form 483 inspection observation report will only include observations that do not relate solely to CGMP requirements. However, if the preliminary assessment is that the compounder's drugs are not exempt under section 503A, the agency may cite CGMP-related observations in the inspection observation report.[49]

Agency Comments

We provided a draft of this report to the Secretary of Health and Human Services. HHS provided written comments, which are reproduced in appendix III. HHS also provided technical comments, which we incorporated as appropriate.

In its comments, HHS stated that FDA has prioritized efforts to increase collaboration between FDA and states regarding oversight of drug compounding, and cited examples of FDA's efforts to do so. HHS also stated that FDA is committed to working with states to further improve communication, noting FDA's efforts to improve communications while

[49]According to agency officials, when FDA's post-inspection review differs from the FDA investigators' preliminary assessment and reveals that a facility does not produce drugs in accordance with the conditions of section 503A, FDA intends to consider citing CGMP violations in any regulatory action it decides to pursue. FDA's notice indicates that, although drug products compounded in accordance with the conditions of section 503A are exempt from certain requirements in the FDCA, they remain subject to all other provisions of the FDCA that apply to conventional drug manufacturers, including, but not limited to, the prohibition on preparing, packing, or holding drugs under insanitary conditions. FDA will continue to include observations on FDA form 483 inspection observation report that appear to constitute insanitary conditions or to violate other requirements from which 503A does not provide an exemption without regard to the investigator's preliminary assessment of a firm's status under section 503A. Department of Health and Human Services, Food and Drug Administration, *Insanitary Conditions at Compounding Facilities, Guidance for Industry, Draft Guidance*, (Silver Spring, Md.: August 2016). See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM514666.pdf, accessed August 26, 2016.

commenting that, in some cases, federal law prohibits the agency from sharing certain information. HHS also acknowledged some of the concerns of states and stakeholders that we noted in our report, including compounding by physicians and access to compounded drugs, and provided information on steps FDA has taken or plans to take regarding these issues.

We are sending copies of this report to the Secretary of Health and Human Services, appropriate congressional committees, and other interested parties. In addition, the report will be available at no charge on the GAO Web site at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs are on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.

Marcia Crosse
Director, Health Care

Appendix I: Information for Purchasers Regarding the Safety and Quality of Compounded Drugs

Representatives of stakeholder organizations we interviewed and states we surveyed identified a number of tools available to purchasers of compounded drugs, including institutional purchasers (e.g., hospitals), health care practitioners (e.g., physicians), and individual patients, that are available for use to determine whether drug compounders are maintaining the appropriate standards for the safety and quality of these drugs.

Examples of tools identified include the following:

- **Food and Drug Administration's (FDA) compounding website:** Purchasers can review FDA's compounding website, which includes information on FDA inspections and actions taken by FDA related to deficiencies found during an inspection. In response to our survey of state pharmacy regulatory bodies, respondents in 13 states reported that they would direct purchasers of compounded drugs to use FDA's compounding website, or other FDA information, in order to determine the safety and quality of compounded drugs.
- **State board of pharmacy websites:** Purchasers can contact their state board of pharmacy or search their state board of pharmacy's website to determine whether the state has inspected a pharmacy, and if so, whether the state had found shortcomings in its compounding operations (for those states that make this information available on their website). Fourteen states reported that they would direct purchasers of compounded drugs to state websites.
- **Pharmacy accreditation organizations:** Purchasers can determine whether a pharmacy was accredited for compounding by an organization, such as the Accreditation Commission for Health Care's Pharmacy Compounding Accreditation Board, or identify whether a pharmacy has met the requirements of other national associations' programs, such as the National Association of Boards of Pharmacy's Verified Pharmacy Program.[1] Six of the 25 stakeholder organizations we talked to indicated that pharmacy accreditation for compounding

[1]As of August 2016, the Accreditation Commission for Health Care's Pharmacy Compounding Accreditation Board had accredited 445 pharmacies. According to officials from the National Association of Boards of Pharmacy, as of August 2016, users from at least 44 jurisdictions utilized information from the Verified Pharmacy Program database, which was developed to enable states to make decisions regarding licensing nonresident pharmacies.

by an organization, such as the Accreditation Commission for Health Care's accreditation board, is a tool that purchasers of compounded drugs can use to assess the safety and quality of compounded drugs.

However, our review found that there were few drug compounders with clean inspections, and relatively few compounders were accredited.[2] Therefore, many purchasers of compounded drugs may rely on information from state and federal regulatory bodies on the safety and quality of compounded drugs, including deficiencies found during inspections.

Institutional purchasers and health care practitioners have additional tools available to identify and evaluate drug compounders as they seek sources to provide compounded drugs for their operations.

- **The American Society of Health-System Pharmacists' assessment tool:** Nine of the 25 stakeholder organizations we talked to referenced the American Society of Health-System Pharmacists' assessment tool, which is intended to help purchasers that choose to outsource the preparation of compounded drugs to evaluate proposals in order to select a drug compounder to supply those drugs.
- **The International Academy of Compounding Pharmacists' Compounding Pharmacy Assessment Questionnaire:** Three of the 25 stakeholder organizations we talked to referenced the International Academy of Compounding Pharmacists' compounding pharmacy assessment questionnaire checklist. This tool was developed based on the U.S. Pharmacopeial Convention's compounding standards, to provide purchasers with a checklist of what to look for in a pharmacy compounding practice.

Other organizations involved in the purchase of prescription drugs—specifically pharmacy benefit managers—may utilize their own tools to help determine whether drug compounders are maintaining the

[2]Of the 75 inspections of outsourcing facilities that FDA conducted from March 5, 2014, through April 22, 2016, FDA issued FDA form 483 inspection observation reports to 85 percent of them. An FDA form 483 inspection observation report is issued to firm management at the conclusion of an inspection when FDA investigators have observed conditions that, in their judgment, may constitute violations of the FDCA and related acts. Of the inspections that did not result in FDA issuing an FDA form 483 inspection observation report, one facility was not yet operational at the time of the inspection.

appropriate standards for the safety and quality of these drugs.[3] For example, officials from one pharmacy benefit manager told us that their organization has developed a credentialing process to evaluate compounding pharmacies for inclusion in their network and to determine the type of compounded drugs these pharmacies may sell in the pharmacy benefit manager's network. The officials said that this process consists of a questionnaire that covers items such as the pharmacy's quality procedures for each compounded dosage form (i.e., it determines whether the pharmacy is capable of accurately making capsules, complex suspensions, and other dosage forms), and the pharmacy's quality practices and procedures. In addition, the officials said they also review the findings from inspections conducted by a state or FDA. At the end of the credentialing process, the organization will establish an agreement with the pharmacy that allows it conduct either "complex nonsterile compounding" or "limited scope nonsterile compounding."[4]

Ten of the 25 stakeholder organizations we talked to indicated that the drug's label is also a tool for patients to use to determine whether the drug is a compounded drug. Outsourcing facilities are required to include a statement on compounded drugs indicating that it is a compounded drug, as well as the drug's expiration date and ingredients.[5] In addition, 24 states reported requiring labeling for compounded drugs, as of January 1, 2016. Therefore, for drugs with such labeling, the patient (if the drug is dispensed directly to a patient) or the provider (if administered in the office or medical facility) could know it was a compounded drug and the expiration date and the ingredients. Section 503A of the Federal Food, Drug, and Cosmetic Act does not require 503A compounders to include a statement that it is a compounded drug on the drugs they

[3]A pharmacy benefit manager is a third-party administrator of prescription drug programs for certain health plans and federal and state government employee plans responsible for developing and maintaining the drug formulary, contracting with pharmacies, negotiating discounts and rebates with drug manufacturers, and processing and paying prescription drug claims.

[4]A complex nonsterile compounding agreement would allow the pharmacy to compound drugs, such as creams with multiple ingredients, and the limited scope nonsterile compounding agreement would allow the pharmacy to compound drugs such as shake lotions (i.e., a lotion that separates into parts with time so it needs to be shaken before use).

[5]21 U.S.C. § 353b(a)(10).

compound. One stakeholder organization pointed out that most labeling is not consistent and that certain drugs may not have a label, such as compounded drugs for hospital patients, or compounded drugs in nuclear pharmacies; another stakeholder organization stated that unless a state requires pharmacies to label compounded drugs as such, patients likely won't know whether the drug was compounded. FDA officials also noted that the agency has heard from stakeholders that physicians and patients may not be aware that the drugs that they are administering or receiving were compounded, or that they are not approved by FDA.

Appendix II: Objectives, Scope, and Methodology

The Drug Quality and Security Act (DQSA), enacted in November 2013, included a provision for GAO to review drug compounding. We examined (1) the settings in which drugs are compounded, and the extent of drug compounding in each state; (2) state laws, regulations, and policies governing drug compounding, and how they are enforced; (3) how communication is conducted between states and FDA, as well as among states, regarding compounding, and any associated challenges; and (4) steps FDA has taken to implement its responsibilities to oversee drug compounding since enactment of the DQSA, and any challenges that have been reported with these efforts. We also examined available information for purchasers of compounded drugs (e.g., hospitals, health systems, and patients) to determine the safety and quality of those drugs.

To address our reporting objectives and obtain information about purchasers of compounded drugs, we administered a web-based survey to the state pharmacy regulatory bodies (e.g., boards of pharmacy) in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands. We interviewed officials at 25 national associations and other stakeholder organizations, government officials in 3 states (Minnesota, North Carolina, and Texas), officials at two pharmacy benefit manager organizations, and officials from the Food and Drug Administration (FDA); and we reviewed relevant documents from FDA and the organizations we interviewed. Finally, to address steps FDA has taken to implement its regulatory responsibilities to oversee drug compounding and related challenges, we reviewed relevant laws and analyzed FDA data on inspections of drug compounders and actions taken related to its inspections of these entities.

2016 Survey of State Pharmacy Regulatory Bodies on Drug Compounding

We administered a web-based survey to the state pharmacy regulatory bodies in the 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands. We surveyed state pharmacy regulatory bodies (states) because these are the entities that regulate pharmacy practice, including drug compounding activities, through state laws and regulations. To collect information on drug compounding across the country, we surveyed all 50 states and the District of Columbia. We also included selected U.S. territories in our survey population—Guam, Puerto Rico, and the U.S. Virgin Islands—because these are the three most populous territories, all have boards of pharmacy, and all are members of the

National Association of Boards of Pharmacy.[1] We primarily obtained contact information for the states from information on boards of pharmacy on the National Association of Boards of Pharmacy's website, and we tested the survey by conducting three pretests of draft versions with officials from a state board of pharmacy in a rural state, officials from a state board of pharmacy in a populous state, and a national pharmacy association.

Our survey was administered from February 8, 2016, through April 15, 2016. We collected information from survey respondents on the settings in which drug compounding occurs and data on drug compounding in each state, state laws, regulations, and policies related to drug compounding, activities states have participated in related to drug compounding with FDA and other states, states' perspectives on communication with FDA and other states, states' perspectives on FDA's implementation of the DQSA, and information on how states would notify purchasers of compounded drugs that a compounded drug was found to be of questionable safety or quality, among other things.

We had a survey response rate of 93 percent; 50 of the 54 states completed the survey. Two states, Alaska and Indiana, responded to some of the survey questions but did not complete the survey; therefore, their responses were not included in our survey analyses. Two of the territories, Puerto Rico and the U.S. Virgin Islands, did not respond to any of the survey questions.

We analyzed the survey responses from the 50 completed surveys and conducted follow up with respondents, as needed, to clarify certain survey responses or obtain additional information.[2] We conducted data checks on the survey responses, including checking for skip patterns and invalid responses, to ensure the reliability of the data.

[1]We refer to all of the state pharmacy regulatory bodies that we surveyed as states in this report.

[2]We relied on state reporting of, and did not independently review, all 50 states' laws, regulations, and policies applicable to drug compounding.

Interviews with Officials in Stakeholder Organizations, State Government Agencies, and FDA

To further address our objectives, we interviewed officials from 25 stakeholder organizations that have a stake or an interest in drug compounding to obtain information such as reviews on the extent of drug compounding; reviews of state laws, regulations, and policies on drug compounding; their perspectives on any challenges in communication between FDA and states, as well as among states, related to drug compounding; and their perspectives on FDA's implementation of the DQSA. We selected these stakeholder organizations to include national organizations representing (1) pharmacies and pharmacists, including those that compound drugs; (2) physicians, including those in medical specialties identified as compounding drugs; and (3) state boards of pharmacy, state medical boards, and state health officials; as well as experts in drug compounding, and an organization that conducted research related to drug compounding.[3] We reviewed relevant documents provided by these stakeholder organizations, including comments submitted to FDA regarding FDA's compounding-related activities.

We also interviewed state agency officials from the boards of pharmacy, medical boards, and the state agencies that have oversight responsibility for outsourcing facilities, in three selected states—North Carolina, Minnesota, and Texas.[4] We selected these states because they reported differing laws, regulations, or policies related to drug compounding in their responses to the survey, which included having different types of state

[3]We interviewed officials from the following 25 national associations and other stakeholder organizations: the Accreditation Commission for Health Care, American Academy of Dermatology, American Academy of Ophthalmology, American Hospital Association, American Medical Association, American Pharmacists Association, American Society of Clinical Oncology, American Society of Consultant Pharmacists, American Society of Health-System Pharmacists, Association of State and Territorial Health Officials, Clinical IQ, Dr. Loyd Allen Jr., Federation of State Medical Boards, Institute for Safe Medication Practices, International Academy of Compounding Pharmacists, the Joint Commission, National Alliance of State Pharmacy Associations, National Association of Boards of Pharmacy, National Association of Chain Drug Stores, National Community Pharmacists Association, National Conference of State Legislatures, National Home Infusion Association, Pew Charitable Trusts, Professional Compounding Centers of America, and the U.S. Pharmacopeial Convention.

[4]Licensed outsourcing facilities are overseen by the North Carolina Department of Agriculture and Consumer Services, Food and Drug Protection Division, in North Carolina, and by the Texas Department of State Health Services, Drugs and Medical Devices Group, in Texas. The Minnesota Board of Pharmacy has oversight responsibilities for licensed outsourcing facilities in Minnesota.

agencies or departments with oversight responsibilities for outsourcing facilities, and variation in their oversight responsibilities of physicians or other nonpharmacists. Through the interviews with the board of pharmacy officials, we obtained additional information on state laws and policies related to drug compounding, as well as additional details for certain survey responses. In our interviews with state medical board officials, we obtained information on the medical board's role in the oversight of drug compounding and other information, as available, related to compounding by physicians in each state. Two of our three selected states—North Carolina and Texas—had a separate state agency responsible for overseeing FDA-registered outsourcing facilities licensed in the state; therefore, we obtained information in these interviews specific to their oversight responsibilities for these facilities. In addition, we interviewed officials from two pharmacy benefit managers—third-party administrators of prescription drug programs for certain health plans and federal and state government employee plans—to obtain information related to drug compounding, including how these entities determine the safety and quality of compounded drugs.[5] The perspectives of the officials from the 25 stakeholder organizations, three selected states, and two pharmacy benefit managers are not generalizable, but provided us with valuable insight on these issues.

We reviewed relevant documents from FDA, including FDA's draft memorandum of understanding (MOU) for use with states regarding distribution of compounded human drug products, and FDA's draft and final guidance related to drug compounding, such as FDA's final guidance on registration of outsourcing facilities. We also reviewed relevant federal laws and regulations related to drug compounding, including sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act. In addition, we interviewed FDA officials and reviewed information on FDA's compounding website to determine steps FDA has taken to implement its regulatory responsibilities to oversee drug compounding since enactment of the DQSA.

[5]The two pharmacy benefit manager organizations that we interviewed were Express Scripts and CVS Caremark. We selected these organizations because they were two of the largest pharmacy benefit managers in the country.

Analysis of FDA Inspections Data

To further address our objective on steps FDA has taken to implement its regulatory responsibilities to oversee drug compounding since enactment of the DQSA, we analyzed FDA data from May 2012 through April 22, 2016, on the number of inspections that FDA has conducted on drug compounders, and data on actions that FDA has taken related to these inspections from May 2012 through June 28, 2016.[6] Actions included FDA issuing an FDA form 483 inspection observation report or a warning letter to an entity.[7] We also obtained FDA data on outsourcing facilities that were currently registered with FDA or have ever been registered with FDA (i.e., facilities that were registered as an outsourcing facility at some point with FDA but are no longer registered) as of April 22, 2016. We determined that the data we used from FDA on inspections and actions related to drug compounding were sufficiently reliable for our purposes by discussing data collection processes and limitations of the data with agency officials, and comparing the data against other published sources.

We conducted this performance audit from May 2015 to November 2016 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

[6]FDA provided inspection data for 503A compounders and outsourcing facilities from May 2012 through April 22, 2016, and data on actions taken from May 2012 through June 28, 2016. We requested FDA inspection data starting in May 2012 because our prior report on drug compounding analyzed this data on 503A compounders up to May 2012, see GAO-13-702. The inspection data we examined on outsourcing facilities started in March 2014 because outsourcing facilities were not created until enactment of the Drug Quality and Security Act in November 2013, and FDA conducted its first inspection in March 2014.

[7]An FDA form 483 is an inspection observation report that is issued at the conclusion of an inspection when FDA investigators have observed conditions that, in their judgment, may constitute violations of the FDCA and related acts. An FDA warning letter is a correspondence that notifies a responsible individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the FDCA, its implementing regulations, and other federal statutes.

Appendix III: Comments from the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES
OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

OCT 19 2016

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, *"DRUG COMPOUNDING: FDA Has Taken Steps to Implement Compounding Law, But Some States and Stakeholders Reported Challenges"* (GAO-17-64).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: DRUG COMPOUNDING: FDA HAS TAKEN STEPS TO IMPLEMENT COMPOUNDING LAW, BUT SOME STATES AND STAKEHOLDERS REPORTED CHALLENGES (GAO-17-64)

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity to review and comment on this draft report. We also appreciate the Government Accountability Office's (GAO) in-depth analysis of the U.S. Food and Drug Administration's (FDA) implementation of the compounding provisions of the law and its interactions with stakeholders, including States, on matters pertaining to drug compounding. While GAO noted some challenges that we address below, we believe that the draft report reflects the significant efforts of FDA over the past several years to develop policies, conduct inspections and take regulatory action, and collaborate with stakeholders to mitigate the risks to the public health from compounded drug products.

FDA believes that effective oversight of human drug compounding requires close collaboration between FDA and the States, and, since 2012, the Agency has prioritized efforts to increase such collaboration. Examples of these efforts include: inviting States to accompany FDA on inspections of State-licensed pharmacies; holding teleconferences with States on various topics, such as to discuss FDA recommendations that a State-licensed pharmacy initiate a recall due to lack of sterility assurance, or to address questions from State officials regarding policy or enforcement matters; and holding monthly meetings with the National Association of Boards of Pharmacy to discuss matters of mutual concern. FDA also holds annual Intergovernmental Working Meetings, most recently on September 21-22, 2016, after GAO's State survey concluded. In response to feedback from prior meetings, FDA changed the format of this meeting to facilitate increased discussion (e.g., through breakout sessions). We received positive feedback from States regarding this most recent meeting.

FDA is pleased that many States provided GAO with positive feedback regarding FDA/State communication, and we are committed to working with States on further improvement. We note that, in some cases, Federal law prohibits FDA from sharing certain information requested by State officials who have not entered into information-sharing agreements with FDA. FDA has encouraged and worked with States and individual State officials to provide such commitments through FDA commissioning pursuant to section 702(a)(1) of the Food, Drug, and Cosmetic Act (FD&C Act or Act) [21 U.S.C. § 372] or information-sharing agreements pursuant to 21 CFR 20.88. For example, FDA created a 5 year, single signature "Long-Term Drug Compounding Information Sharing Agreement," to improve communications and facilitate oversight of compounding pharmacies. FDA also created a chart, "Compounding Domestic Inspection Information Sharing Chart," to describe categories of information that are gathered during or after an FDA inspection, the types of non-public information that might be included in the various categories of information, and the conditions under which such non-public information can be shared with a State. Both documents are available on FDA's website.

FDA is aware of the concerns identified in GAO's report associated with physician compounding, including the lack of State oversight over this activity in many cases. FDA is engaging in discussions with the Federation of State Medical Boards and other organizations concerning physician compounding, and, in the future, we intend to offer guidance and educational outreach concerning provisions of Federal law that apply to physician compounding. For example, FDA's August 2016 draft guidance, *Insanitary Conditions at Compounding*

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: HIGH-CONTAINMENT LABORATORIES: IMPROVED OVERSIGHT OF DANGEROUS PATHOGENS NEEDED TO MITIGATE RISK (GAO-16-642)

Facilities, provides examples of conditions that FDA considers to be "insanitary." This draft guidance clarifies that compounded drugs, including drugs compounded by physicians, are adulterated in violation of Federal law if they are prepared, packed, or held under insanitary conditions whereby they may become contaminated with filth or rendered injurious to health. In addition, FDA held a session during its most recent Intergovernmental Working Meeting in September 2016, concerning challenges associated with oversight of physician compounding.

FDA also recognizes the concerns raised by representatives from certain States and stakeholder organizations concerning access to compounded drugs. As FDA implements the compounding provisions of the FD&C Act, we are committed to establishing policies that preserve access to compounded drugs for patients who need them, while protecting patients from receiving poor quality compounded drugs that could cause serious harm. After the 2012 fungal meningitis outbreak that resulted in over 60 deaths and over 750 cases of infection in patients in 20 States, Congress passed the Drug Quality and Security Act, establishing a new category of compounders called "outsourcing facilities" that may compound and distribute drugs without first receiving patient-specific prescriptions, but that are subject to increased Federal oversight and quality standards. Outsourcing facilities engage in compounding of sterile and non-sterile drugs, small and large batches, and with and without first receiving patient-specific prescriptions. Health care facilities that need non-patient specific compounded drugs to meet patients' medical needs should obtain those drugs from outsourcing facilities.

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse (202) 512-7114 or crossem@gao.gov

Staff Acknowledgments

In addition to the contact above, Kim Yamane (Assistant Director), Lisa A. Lusk (Analyst-in-Charge), Matthew Byer, Julie Flowers, Sandra George, and Drew Long made key contributions to this report.