



February 2015

DRUG SHORTAGES

Better Management of
the Quota Process for
Controlled
Substances Needed;
Coordination between
DEA and FDA Should
Be Improved

GAO Highlights

Highlights of [GAO-15-202](#), a report to congressional requesters

Why GAO Did This Study

In the last decade, shortages of prescription drugs containing controlled substances, such as narcotics and stimulants, have increased nationwide, preventing providers and patients from accessing essential medications for treatment. Controlled substances are regulated by DEA because of the potential for abuse and addiction. To prevent diversion of controlled substances, DEA sets quotas that limit the amount of certain substances that are available in the United States.

GAO was asked to examine shortages of drugs containing controlled substances. This report examines (1) the trends in such shortages, (2) the effect on patients and providers, (3) DEA's administration of the quota process, and (4) coordination between DEA and FDA to prevent and mitigate shortages. GAO analyzed data from 2001 through 2013 from the University of Utah Drug Information Service, which is generally regarded as the most comprehensive source of drug shortage data, and from 2011 and 2012 from YERS/QMS, which is the official record for the quota process. GAO interviewed officials from DEA, FDA, organizations representing patients and providers, and drug manufacturers. GAO reviewed relevant statutes, regulations, and documents.

What GAO Recommends

DEA should take five actions to improve its management of the quota process; DEA and FDA should quickly update their MOU and agree on steps each will take regarding drug shortages. HHS agreed with the applicable recommendations. DEA neither agreed nor disagreed, but raised multiple objections to this report.

View [GAO-15-202](#). For more information, contact Marcia Crosse at (202) 512-7114 or crosse@gao.gov.

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Better Management of the Quota Process for Controlled Substances Needed; Coordination between DEA and FDA Should Be Improved

What GAO Found

Shortages of prescription drugs containing controlled substances have increased sharply in recent years; of the 168 shortages reported from January 2001 through June 2013, nearly 70 percent began after 2007. Such shortages lasted for nearly a year, on average. Additionally, many shortages involved generic pain relievers and drugs where there was only one manufacturer.

The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), and organizations representing patients and providers report that during shortages of drugs containing controlled substances, patients may receive less effective care, experience medication errors, or not receive treatment at all. They said providers are also affected as they spend time and resources mitigating the effects of shortages, rather than providing care.

The Drug Enforcement Administration (DEA), an agency within the Department of Justice (DOJ), has not effectively administered the quota process that limits the amount of controlled substances available for use in the United States. Each year, manufacturers apply to DEA for quota needed to make their drugs. DEA, however, has not responded to them within the time frames required by its regulations for any year from 2001 through 2014. DEA officials attributed this lack of compliance to inadequate staffing. Manufacturers who reported quota-related shortages cited late quota decisions as causing or exacerbating shortages of their drugs. Additionally, DEA's weak internal controls jeopardize the agency's ability to effectively manage the quota process. For instance, agency officials said that DEA does not conduct quality checks to ensure the accuracy of the data in its Year-End Reporting and Quota Management System (YERS/QMS). GAO estimates that 44 percent of YERS/QMS records in 2011 and 10 percent in 2012 had errors. DEA officials said that 2011 was the first year manufacturers applied for quota electronically and they expected data from 2012 and beyond to be more accurate. DEA also lacks critical management information because it does not have performance measures related to setting quotas, nor does it monitor data to assess its performance. Moreover, DEA does not have reasonable assurance that the quotas it sets are in accordance with its requirements and cannot ensure continuity of its operations, as it does not have protocols, policies, training materials, or other documentation to manage the quota process.

Despite statutory provisions requiring DEA and FDA to coordinate certain efforts to address shortages of drugs containing controlled substances, the agencies have not established a sufficiently collaborative relationship. For example, DEA and FDA disagree about what constitutes a shortage. DEA officials also said that they do not believe FDA appropriately validates or investigates the shortage information it posts on its website and that posting this information encourages manufacturers to falsely report shortages to obtain additional quota. However, FDA reports that it takes steps to investigate and confirm the shortages on its website. Given such barriers to coordination, DEA and FDA cannot effectively act to prevent or alleviate shortages. Although DEA and FDA have a memorandum of understanding (MOU) in place, it has not been revised since the 1970s and they have been working for more than two years to update it. Officials from both agencies said an updated MOU could facilitate information sharing and help prevent and mitigate future shortages of drugs containing controlled substances.

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Abbreviations

ADHD	attention deficit hyperactivity disorder
API	active pharmaceutical ingredient
APQ	aggregate production quota
ARCOS	Automation of Reports and Consolidated Orders System
CSA	Controlled Substances Act
DEA	Drug Enforcement Administration
DOJ	Department of Justice
DSS	Drug Shortage Staff
EMS	emergency medical services
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GPRA	Government Performance and Results Act of 1993
HHS	Department of Health and Human Services
MOU	memorandum of understanding
UUDIS	University of Utah Drug Information Service
YERS/QMS	Year-End Reporting and Quota Management System

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February 2, 2015

The Honorable Charles E. Grassley
Chairman
Committee on the Judiciary
United States Senate

The Honorable Sheldon Whitehouse
Ranking Member
Subcommittee on Crime and Terrorism
Committee on the Judiciary
United States Senate

In the last decade, shortages of prescription drugs have increased nationwide, preventing providers and patients from accessing medications that are essential for treatment. Some shortages involve drugs that contain controlled substances, such as narcotics, stimulants, and sedatives, which play an important role in health care.¹ For example, anesthesia, which is used to sedate patients, is routinely administered prior to surgical procedures and most patients receive some kind of drug containing a controlled substance during inpatient hospital stays. Emergency medical service (EMS) providers also frequently rely on a variety of drugs containing controlled substances to treat patients experiencing heart attacks, seizures, traumatic injuries, and other medical crises. For example, data from the National EMS Information System, a nationwide repository of information collected by EMS organizations, show that fentanyl and morphine—both narcotics that are used to manage pain—were 2 of the 10 most frequently administered medications by such organizations in 2012. In addition, some drugs containing controlled substances are available by prescription for outpatient use as pain relievers or sleep aids, as well as to treat individuals with attention deficit hyperactivity disorder (ADHD) and anxiety. During shortages, providers—including hospitals, physicians, and pharmacists—may have to use alternative medications, if alternatives are available at all. The Food and Drug Administration (FDA), an agency within the Department of

¹A controlled substance is one that is included in one of five schedules under the Controlled Substances Act. A controlled substance is placed in a respective schedule based on whether it has a currently accepted medical use in the United States and its potential for abuse and physical or psychological dependence. 21 U.S.C. §§ 802(6), 812.

Health and Human Services (HHS), which oversees the safety and effectiveness of drugs marketed in the United States, considers drug shortages to be a serious public health concern and works to prevent, alleviate, and resolve them.²

Despite their medical value, prescription drugs containing these substances have the potential for abuse and psychological and physical dependence. They are therefore required to be regulated by the Drug Enforcement Administration (DEA), an agency within the Department of Justice (DOJ), in accordance with the Controlled Substances Act (CSA). The Centers for Disease Control and Prevention has declared that the United States is in the midst of an epidemic of prescription drug overdose deaths. In 2011, more than 22,000 Americans died from drug overdoses attributable to prescription drugs, and most of those deaths—almost 17,000—were due to prescription pain relievers containing controlled substances. To prevent diversion of controlled substances, DEA maintains a closed system of distribution, which includes limiting the amount of certain controlled substances that are available. To do so, DEA establishes quotas for the maximum amount of each basic class of controlled substance—such as amphetamine or morphine—that can be produced each year in the United States, known as aggregate production quotas (APQ). It also establishes quotas for individual manufacturers, who must apply to DEA to obtain quota for specific classes of controlled substances. In setting quotas, DEA is required to provide for the estimated medical, scientific, research, and industrial needs of the United States.³

You raised questions about shortages of drugs containing controlled substances and asked us to examine the effect of such shortages on patients. You also asked us to review DEA's administration of the quota process to understand its potential effects on shortages of drugs containing controlled substances, particularly those used by EMS

²We have previously reported on trends in the number of drug shortages and types of drugs most often in shortage, the causes of such shortages, and FDA's ability to respond to them. GAO, *Drug Shortages: FDA's Ability to Respond Should Be Strengthened*, [GAO-12-116](#) (Washington, D.C.: Nov. 21, 2011), and *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability*, [GAO-14-194](#) (Washington, D.C.: Feb. 10, 2014).

³In addition, DEA is also required to provide for lawful export requirements, and for the establishment and maintenance of reserve stocks. 21 U.S.C. § 826; 21 C.F.R. § 1303.11.

providers and to treat ADHD. This report (1) identifies the trends in shortages of drugs containing controlled substances that occurred from January 2001 through June 2013, (2) describes the reported effects of shortages of drugs containing controlled substances on patients and providers, (3) examines DEA's administration of the quota process for controlled substances, and (4) examines DEA and FDA coordination activities to prevent and mitigate shortages of drugs containing controlled substances.

To identify the trends in shortages of drugs containing controlled substances from January 2001 through June 2013, we analyzed University of Utah Drug Information Service (UUDIS) data during this time period.⁴ UUDIS data is generally regarded as the most comprehensive and reliable information on drug shortages for the time period we reviewed and are what we used in preparing our 2011 and 2014 reports on drug shortages.⁵ For this report we used an extract of the UUDIS dataset used to prepare our 2011 and 2014 reports, which covered shortages from 2001—the first year available from UUDIS—through June 2013. We also examined the characteristics of drugs containing controlled

⁴UUDIS broadly defines a shortage as a supply issue that affects how pharmacies prepare and dispense a product or that influences patient care when prescribers must choose an alternative therapy because of supply issues. Once UUDIS identifies a shortage, it generally does not consider a shortage to be resolved until the drug is available again in all strengths and package sizes from all manufacturers that currently produce the drug. For example, UUDIS could be notified of a shortage involving three manufacturers: Manufacturer A has no product available; Manufacturers B and C still do, but have limited supply of certain package sizes. According to a UUDIS official, UUDIS would consider the shortage to be resolved (1) when Manufacturers A, B, and C all have all strengths and package sizes back in stock; (2) if Manufacturer A decides to discontinue its product, when Manufacturers B and Manufacturer C both have all strengths and package sizes back in stock; or (3) when UUDIS obtains other information indicating that a shortage has been resolved, such as FDA telling UUDIS that Manufacturers B and C have increased supply and all market need has been met. Our analysis focuses on shortages of prescription drugs, so we excluded shortages of over-the-counter drugs, biologics (including vaccines), medical devices, and orally administered vitamins from our analysis even though UUDIS also tracks and includes these shortages in its data.

⁵See [GAO-12-116](#) and [GAO-14-194](#). At the time we did work for our 2011 report, FDA did not have a database containing information on drug shortages. Since then, FDA developed its own database to track shortages. We reported concerns with FDA's management of this database in 2014, see [GAO-14-194](#). For this report, we used the drug shortage data maintained by UUDIS because the time period we reviewed includes years that predate the development of FDA's database. It also allows us to provide information on the trends and characteristics of drug shortages comparable to that which we presented in our 2011 and 2014 reports.

substances that were in shortage at some point from January 2001 through June 2013 and that UUDIS identified as critical shortages because alternative medications were unavailable, the shortages affected multiple manufacturers, or the shortages were widely reported. These critical shortages were a subset of the total number of shortages reported during this time period.⁶ For this subset of shortages, we obtained drug shortage bulletins created by UUDIS, which contain national drug codes associated with each shortage.⁷ Using these national drug codes, we analyzed Red Book data to determine the product types, routes of administration, and therapeutic classes.⁸ We reviewed all UUDIS data for reasonableness, outliers, and consistency, and based on our review we determined that the data were sufficiently reliable for our purposes. Additionally, to give context to and inform these analyses we interviewed officials at the FDA and UUDIS. For this objective as well as our remaining objectives, the scope of our work was limited to prescription drugs, as opposed to over-the-counter or behind-the-counter medications.

To describe the reported effects of shortages of drugs containing controlled substances on patients and providers, we interviewed officials from provider and patient organizations, such as the American Society of Anesthesiologists and Children and Adults with Attention Deficit/Hyperactivity Disorder. We selected provider and patient organizations that represent populations we determined were likely to be affected by shortages of drugs containing controlled substances. The information that we obtained from these organizations is not generalizable to all provider and patient organizations, but provided us with valuable insights. For a complete list of patient and provider organizations we interviewed, see appendix I. We also interviewed officials from FDA, the

⁶These shortages represented 52 percent of all shortages of drugs containing controlled substances reported during this period.

⁷UUDIS creates a drug shortage bulletin for all shortages that it identifies as critical. Each bulletin is publically posted on the American Society of Health-System Pharmacists' website and describes the reason for the shortage; any estimated resupply dates; any related shortages; and the national drug codes associated with the shortage. A national drug code is a unique identifier, though one drug can have multiple national drug codes associated with it. For example, a drug made by one manufacturer, in one strength, but in three package sizes would have a different national drug code for each of the three package sizes. UUDIS does not consistently track the national drug codes associated with shortages that it has determined are not critical.

⁸Red Book is a compendium published by Truven Health Analytics that includes information about the characteristics of drug products.

Office of the Assistant Secretary for Preparedness and Response within HHS, and the National Highway Traffic Safety Administration's Office of Emergency Medical Services. We reviewed relevant documentation from these organizations and agencies, including the results of surveys they had conducted of their constituencies.

To examine DEA's administration of the quota process for controlled substances, we reviewed the CSA and DEA's regulations and other documentation regarding the agency's process for establishing quotas for certain classes of controlled substances with medical use.⁹ See appendix II for the specific substance classes subject to quotas that we considered to have medical use. We also interviewed DEA officials about the quota process, including factors that affect the agency's timeliness and responsiveness to manufacturers' quota applications. In addition, we reviewed DEA's administration of the quota process in light of relevant federal standards for internal controls and our prior work related to the establishment of agency performance measures.¹⁰ To examine the timeliness of DEA's quota decisions for certain classes of controlled substances, we reviewed Federal Register notices for APQs for years 2001 through 2014. From our review of Federal Register notices, we were also able to determine when DEA established annual quotas for individual manufacturers from 2001 through 2014, as these types of quota are established after the APQ has been established in the Federal Register. We also analyzed data from the system DEA uses to track and record quota applications and decisions—the Year-End Reporting and Quota Management System (YERS/QMS). We analyzed data for certain controlled substances with medical use from 2011 and 2012, the most recent years for which data were available when we began our work. We

⁹We consider certain classes of controlled substances with medical use to be those substances subject to quotas that are contained in FDA-approved products that are currently marketed for human use.

¹⁰See GAO, *Standards for Internal Control in the Federal Government*, [GAO/AIMD-00-21.3.1](#) (Washington, D.C.: November 1999). Among other things, these standards address the need for federal agencies to establish internal controls and to monitor the performance of their programs. The establishment and review of performance measures and indicators is a control activity. Monitoring internal controls allows agencies to assess the quality of performance over time. We have also reported on the importance of establishing performance measures that demonstrate how well a program is achieving its goals. See GAO, *Executive Guide: Effectively Implementing the Government Performance and Results Act*, [GAO/GGD-96-118](#) (Washington, D.C.: June 1996).

analyzed the source documents for a stratified random sample of 440 YERS/QMS records from 2011 and 2012 (15 percent of the total records during these years for certain controlled substances with medical use). We used these source documents to verify YERS/QMS data, each of which includes a manufacturer's quota application for a particular substance and the corresponding decision letter from DEA informing the manufacturer of its quota authorization. We compared the information in these documents with corresponding YERS/QMS records and found many instances of discrepancies between them. We therefore determined the data from YERS/QMS to be unreliable for the purposes of our review, and so we instead are reporting on our analysis of the information contained in the source documents for our sample of YERS/QMS records to determine DEA's timeliness in responding to manufacturers' quota applications. See appendix III for additional information on the sample design and methodology we used to determine the reliability of the data and to report on the source documents. We then compared the timing of DEA's quota decisions, both for the APQs and manufacturers' quotas, to required deadlines in the CSA and DEA's regulations. In addition, we interviewed manufacturers about their experiences with DEA's quota process, including any effect the quota process may have had on shortages of their products. We also reviewed documentation provided by manufacturers about their quota applications and DEA's responses. Specifically, we spoke with 13 dosage form manufacturers, including 7 that had the greatest number of drugs containing controlled substances subject to quota in shortage from January 2010 through June 2013.¹¹ We also spoke with 2 bulk manufacturers that supplied active pharmaceutical ingredients (API) for some of the drugs containing controlled substances that were in shortage.¹² We identified these manufacturers through our analysis of FDA data on the manufacturer-reported causes of shortages

¹¹Dosage form manufacturers produce drugs in finished dosage form, which is a drug product in the form in which it will be administered to a patient, such as a tablet or capsule. Finished dosage forms are manufactured using active pharmaceutical ingredients, such as controlled substances, and excipients, such as fillers or preservatives. An active pharmaceutical ingredient is any element that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body. An excipient is an inactive ingredient or component that is not the active pharmaceutical ingredient and serves as the vehicle or medium for the active ingredient.

¹²Bulk manufacturers produce API from raw materials for use by dosage form manufacturers in making finished dosage forms for consumption. For example, bulk manufacturers may obtain poppy raw materials to manufacture morphine API.

of drugs containing controlled substances from January 2010 through June 2013, the most recent years for which data were available when we began our analysis. We reviewed FDA's data for reasonableness, outliers, and consistency, and based on our review, determined that the data were sufficiently reliable for our purposes. Lastly, we interviewed DEA and FDA officials about the causes of shortages of drugs containing controlled substances.

To examine DEA and FDA coordination activities to prevent and mitigate shortages of drugs containing controlled substances, we reviewed the relevant provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA) as well as other documentation governing how the two agencies are to coordinate.¹³ We interviewed DEA and FDA officials about their coordination activities. In addition, we reviewed our past work related to interagency collaboration and the necessary elements for a collaborative working relationship.¹⁴

We conducted this performance audit from October 2012 through February 2015 in accordance with generally accepted government auditing standards.¹⁵ 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 the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

¹³Pub. L. No. 112-144, tit. X, 126 Stat. 993, 1099-1108 (2012).

¹⁴See GAO, *Results-Oriented Government: Practices That Can Help Enhance and Sustain Collaboration among Federal Agencies*, [GAO-06-15](#) (Washington, D.C.: Oct. 21, 2005). For that report, we reviewed relevant literature and interviewed experts in the area of collaboration to identify key practices that can help enhance and sustain federal agency collaboration.

¹⁵Completion of our audit was delayed significantly because of DEA's refusal to comply with our requests for information from and about YERS/QMS for over a year. We requested access to YERS/QMS materials and data starting in January 2013, but did not obtain needed information until March 2014.

Background

DEA's Oversight of Controlled Substances

Within DEA, the Office of Diversion Control is responsible for preventing, detecting, and investigating the diversion of controlled substances. The mission of this Office is dually focused on preventing diversion while ensuring an adequate and uninterrupted supply of these substances for legitimate needs. The CSA requires DEA to maintain a closed system of distribution of controlled substances in the United States from the point of import and manufacture through dispensing to patients or disposal. DEA funds diversion control activities, including the quota process, through fees that it sets for businesses, individuals, or entities that are required to register with DEA to import, export, manufacture, distribute, dispense, or conduct research on controlled substances.¹⁶ The CSA requires that DEA set registration fees at a level that ensures DEA recovers the full costs of operating its Diversion Control Program.¹⁷ DEA adjusts registration fees through the notice and comment rulemaking process and last adjusted registration fees in March 2012.¹⁸

The CSA places each controlled substance in one of five schedules based on whether the substance has a currently accepted medical use in treatment in the United States, its relative potential for abuse, and the degree of dependence the drug or other substance may cause.¹⁹ Schedule I controlled substances, such as heroin and LSD, have a high potential for abuse and no currently accepted medical use in treatment in

¹⁶Diversion control activities refer to activities related to the registration and control of the manufacture, distribution, dispensing, importation, and exportation of controlled substances and listed chemicals. 21 U.S.C. § 886a(2)(B). See 21 C.F.R. pt. 1301 for more information on DEA's registration requirements and fees.

¹⁷21 U.S.C. § 886a.

¹⁸DEA's March 2012 registration fee adjustment took place nearly 6 years after its prior adjustment. Controlled Substances and List I Chemical Registration and Reregistration Fees, 77 Fed. Reg. 15234-15250 (Mar. 15, 2012).

¹⁹In addition to DEA's role in regulating controlled substances, states may also establish laws that regulate controlled substances. State laws must be in accordance with the CSA, but may be more restrictive.

the United States.²⁰ Schedule II controlled substances have a high potential for abuse, which may lead to severe psychological or physical dependence, but also have a currently accepted medical use; for instance, amphetamine is a schedule II controlled substance and is used to treat ADHD. As part of the closed system of distribution to prevent the diversion of controlled substances, the CSA requires DEA to establish quotas for each basic class of schedule I and II controlled substances.²¹ Quotas are not established for schedule III, IV, and V controlled substances, which have a currently accepted medical use, a lower potential for abuse, and a lower physical and psychological dependence relative to schedule I and II controlled substances.²²

DEA's Process for Establishing Quotas for Certain Controlled Substances

Each year the Office of Diversion Control establishes three types of quotas for schedule II substances: APQs, bulk manufacturing quotas, and procurement quotas.²³ Within the Office of Diversion Control, the Quota Unit is responsible for calculating and proposing quotas that are then established by the agency.²⁴

Aggregate production quotas, which are established for each basic class of schedule I and II substances—such as amphetamine or

²⁰Although schedule I substances have no accepted medical use in the United States, DEA issues quotas for these substances for scientific, industrial, and research purposes, including clinical trials. We do not include schedule I substances in our review of DEA's quota process because they have no accepted medical use in the United States.

²¹In addition to each basic class of schedule I and II substances, DEA is also mandated to establish quotas for list I chemicals ephedrine, pseudoephedrine, and phenylpropanolamine. 21 U.S.C. § 826. In setting quotas for these chemicals, DEA establishes an assessment of annual needs, which is to provide for the estimated medical, scientific, research, and industrial needs of the United States, lawful export requirements, and the establishment and maintenance of reserve stocks. Registrants apply for import quotas to import list I chemicals in to the United States. We did not include quotas for list I chemicals within the scope of this report because DEA officials said that only a small amount of these substances are used to manufacture schedule II substances.

²²These schedules include drugs such as Tylenol with codeine®, Valium®, and Xanax®.

²³Although DEA's regulations use the term "individual manufacturing quotas," DEA officials refer to them as "bulk manufacturing quotas." Accordingly, we use the term "bulk manufacturing quotas" throughout our discussion. Companies that obtain bulk manufacturing quotas register with DEA as bulk manufacturers.

²⁴In this report, we refer to the Office of Diversion Control's UN Reporting and Quota Section as the Quota Unit.

morphine—specify the maximum amount of each controlled substance that can be manufactured in the United States in a given year to provide for the estimated medical, scientific, research, and industrial needs of the United States, lawful export requirements, and the establishment and maintenance of reserve stocks. APQs limit the amount of bulk materials that may be manufactured or synthesized in the United States, and subsequently available for use in the manufacture of drug products containing schedule I and II controlled substances. In establishing APQs for each basic class of schedule I and II controlled substances, DEA considers information from many sources, including

- manufacturers' production history and anticipated needs;
- estimates from IMS Health on retail consumption based on prescriptions dispensed;²⁵
- data from DEA's internal system for tracking controlled substances transactions, known as the Automation of Reports and Consolidated Orders System (ARCOS);
- past histories of quota granted for each substance from YERS/QMS;
- estimates of the projected medical, scientific, and reserve stock needs provided by FDA's Controlled Substances Staff;²⁶
- information regarding new and discontinued drug products containing schedule II substances from FDA; and
- data on the diversion of controlled substances, such as information from case seizures and national databases of drug evidence.

By May 1 of each year, DEA is required to propose APQs in the Federal Register for the next year and mail a copy of its proposal to persons registered as bulk manufacturers of the basic class.²⁷ Any interested person may file comments on or objections to the notice, and, after consideration of such comments or objections, DEA must then establish APQs in the Federal Register and mail a copy of its decisions to

²⁵DEA obtains prescription data from IMS Health, a company that collects and analyzes health care data, to determine the number of prescriptions and total amount of drugs purchased by retail establishments for dispensing for each substance.

²⁶FDA also uses data from IMS Health to develop its estimates of projected use in the United States.

²⁷21 C.F.R. § 1303.11.

manufacturers of the basic class.²⁸ DEA may increase or decrease the APQ at any point due to fluctuations in demand and other factors, such as changes in accepted medical use of a substance for treatment or availability of raw materials for use in manufacturing.²⁹ DEA monitors the various data sources used to establish the APQ, as well as an FDA website containing information on drug shortages, to identify any possible changes in supply.³⁰ Generally, the agency revises the APQ midway through the year to account for any of these changes, as well as to account for any changes in anticipated need communicated by quota applicants. The process for revising the APQ is similar to the one used to establish it. Beginning with 2013 APQs, DEA established an additional 25 percent reserve in APQs in the event of natural disaster or other unforeseen event that could result in substantial disruption to the amount of basic classes of schedule II substances available for manufacture.

Bulk manufacturing quotas limit the amount of a basic class of schedule I or II controlled substance that an individual bulk manufacturer can manufacture through the extraction or synthesis of plant material or other controlled substances. Each bulk manufacturer must apply to DEA to obtain bulk manufacturing quota for a specific substance class and the bulk manufacturing quotas granted to manufacturers in sum cannot exceed the APQs established by DEA.

Procurement quotas limit the amount of a basic class of schedule I or II controlled substance that an individual manufacturer can procure from a manufacturer of bulk raw materials in order to manufacture into dosage forms of a drug or into other substances.³¹ The sum of procurement quotas determines the amount of bulk material that needs to be produced.

²⁸21 C.F.R. § 1303.11. See e.g., Controlled Substances: Established Aggregate Production Quotas for 2012, 76 Fed. Reg. 78044 (Dec. 15, 2011).

²⁹21 C.F.R. § 1303.13.

³⁰DEA also monitors letters and telephone calls it receives from individuals who indicate that they cannot get their prescriptions filled for specific products or drugs from their local pharmacies.

³¹We refer to companies that obtain procurement quotas as dosage form manufacturers.

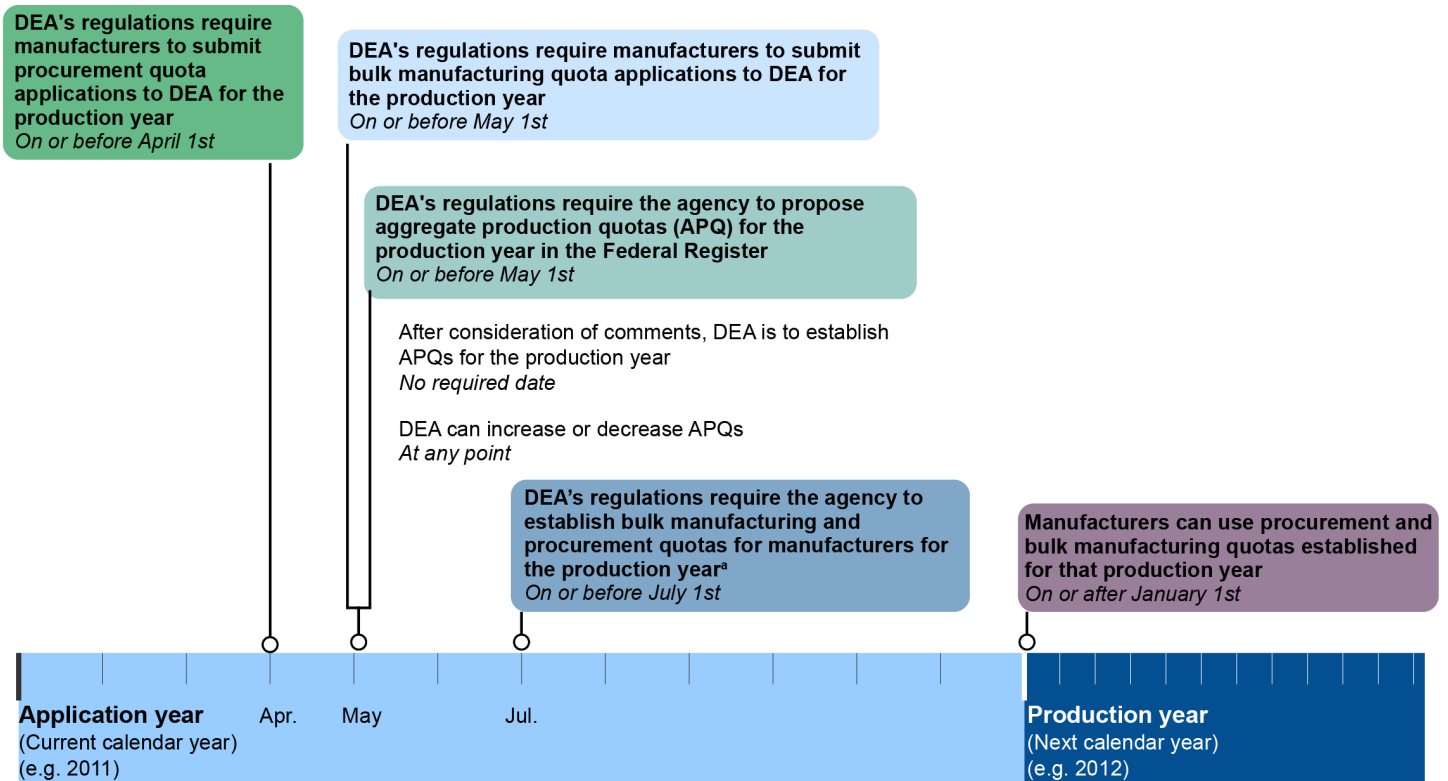
DEA does not have the authority to issue quotas for specific products or to require manufacturers to use their quota for specific products, but rather establishes the quotas for the basic class of controlled substance. For example, DEA may grant a quota of 10,000 grams of amphetamine to a manufacturer, but it is up to the manufacturer to determine how much of that quota will be put towards the various strengths and formulations of its drug products.

In establishing bulk manufacturing and procurement quotas for individual manufacturers, DEA considers the same types of information it uses to establish APQs. However, the agency's focus in reviewing the information is relative to the requesting manufacturer for that particular substance, rather than the total annual need, as is done for the APQ.

The CSA and DEA's implementing regulations designate specific dates by which manufacturers must apply for quotas, as well as dates by which DEA must establish quotas (see fig. 1). Manufacturers apply for quotas in the current year, which we term the application year. Their application is for use of the quota in the next calendar year, which we term the production year. Manufacturers may request a revision to their bulk manufacturing or procurement quota at any point.³² When manufacturers apply for a revision to their quota during the production year, we term this a supplemental quota application.

³²21 C.F.R. §§ 1303.12(d), 1303.25(a). DEA also may at any time reduce a manufacturer's bulk manufacturing quota to prevent exceeding the APQ. 21 C.F.R. § 1303.26.

Figure 1: Timeline for Manufacturers to Apply for Quotas and for the Drug Enforcement Administration (DEA) to Propose or Establish Quotas



Source: GAO analysis of the Controlled Substances Act (CSA) and DEA's regulations. | GAO-15-202

Notes: Unused quota from one year cannot be carried over to the following production year. For example, any remaining quota authorized for 2011 cannot be used to obtain controlled substances for procurement quotas and cannot be used to manufacture controlled substances for bulk manufacturing quotas in 2012. A bulk manufacturer, however, may extract or synthesize active pharmaceutical ingredient in one year and hold it in inventory until any subsequent year.

Pursuant to section 1005 of the Food and Drug Administration Safety and Innovation Act, DEA is to review quota requests from manufacturers that relate to shortages of drugs containing schedule II controlled substances and respond within 30 days. Pub. L. No. 112-144, 126 Stat. 993, 1105 (2012) (codified at 21 U.S.C. § 826(h)). Manufacturers can apply to DEA for more quota at any point, but there is no required time frame for DEA to respond to such supplemental quota requests unless a request relates to a drug in shortage.

^aIn contrast to DEA's regulations, the CSA requires DEA to issue bulk manufacturing quotas to manufacturers on or before October 1 for the production year. 21 U.S.C. § 826(c).

DEA launched an electronic system, known as YERS/QMS, in 2008 for manufacturers to submit end of year reports to the agency. Starting in 2011, manufacturers were able to use YERS/QMS to submit quota

applications to the agency electronically.³³ YERS/QMS serves as the official record for the quota process. The system allows DEA to track manufacturers' quota applications—including the date of the quota application, the amount of quota requested, the amount of quota previously authorized by DEA in prior years, and information about the products that will be manufactured with the requested quota—throughout its review process within the Office of Diversion Control. Additionally, YERS/QMS records DEA's decision about how much quota to authorize and the date on which DEA sends a decision letter to the manufacturer notifying it of the agency's quota decision.

FDA's Role in Preventing and Resolving Drug Shortages and Coordination with DEA

Consistent with its mission of protecting public health, FDA established the Drug Shortage Program in 1999—now known as the Drug Shortage Staff (DSS)—to help prevent, alleviate, and resolve shortages. DSS compiles information on drug shortages received from manufacturers and the public, including the reasons for the shortages.³⁴ FDA defines a shortage as a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug.³⁵ DSS verifies the existence of a shortage by (1) determining if the current demand for a product is stable or increasing based on historical data from IMS Health; (2) contacting all manufacturers of a given drug to investigate supply issues and to obtain information on inventory, manufacturing schedules, and any changes to ordering patterns; (3) evaluating product distribution at the wholesale level, if needed; and (4) assessing information obtained from IMS Health, manufacturers, and wholesalers for the particular product reported to have a potential or actual shortage

³³Manufacturers can also submit hard copy paper applications by mail, in which case DEA officials will then manually enter the information from the applications into YERS/QMS.

³⁴With the enactment of FDASIA, manufacturers must notify FDA at least 6 months prior to the date of a discontinuance or interruption (or as soon as possible if 6 months is not feasible) in the manufacture of a drug that is life supporting, life sustaining, or used to treat debilitating health issues. Pub. L. No. 112-144, § 1001, 126 Stat. at 1099 (codified at 21 U.S.C. § 356c(a)-(b)).

³⁵Pub. L. No. 112-144 § 1001, 126 Stat. at 1100 (codified at 21 U.S.C. § 356c(h)(2)). In September 2014, FDA changed its definition of a drug shortage to be consistent with FDASIA. According to FDA, this is not a substantive change in definition and does not alter how FDA works on matters regarding drug shortages. In general, FDA focuses on shortages of medically necessary drugs that have a significant effect on public health.

and for any acceptable alternative products.³⁶ DSS tracks drug shortages until their resolution, and posts information on its website about current and resolved shortages. FDA also obtains information from the American Society of Health-System Pharmacists, which becomes aware of drug shortages through voluntary reporting from hospitals, pharmacists, and other health care providers. FDA responds to shortages by taking actions within its authority to address the underlying causes and to enhance product availability. For example, FDA may offer feedback on a manufacturers' proposed approach to responding to quality concerns.

FDASIA, enacted in July 2012, contains several provisions related to drug shortages that require coordination between FDA and DEA. When FDA is notified of a supply disruption of a drug that is life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, and that contains a controlled substance subject to quotas, FDASIA requires that FDA request, if FDA determines that it is necessary, that DEA increase quotas applicable to that controlled substance.³⁷ Similarly, when FDA has determined that a schedule II drug is in shortage in the United States, manufacturers may also make such requests by submitting quota applications and FDASIA requires that DEA respond to these requests from manufacturers within 30 days.³⁸ Regardless of whether the request came from FDA or manufacturers, if DEA determines that issuing additional quota is not necessary to address a shortage it must provide a written response, which FDA is to post on its website.³⁹

Additionally, FDASIA requires both FDA and DEA to describe their coordination on efforts to prevent or alleviate drug shortages in annual reports to Congress.⁴⁰ FDASIA also requires FDA to maintain an up-to-

³⁶FDA, *Manual of Policies and Procedures, Drug Shortage Management*, MAPP 4190.1, Rev. 2, (Sept. 3, 2014).

³⁷Pub. L. No. 112-144, § 1001, 126 Stat. at 1099-1100 (codified at 21 U.S.C. § 356c).

³⁸This requirement applies where the manufacturer's request pertains to a schedule II controlled substance that is on the list of drugs in shortage maintained by FDA under section 506E of the Federal Food, Drug, and Cosmetic Act (established by section 1004 of FDASIA). Pub. L. No. 112-144, § 1005, 126 Stat. at 1105 (codified at 21 U.S.C. § 826(h)).

³⁹Id. §§ 1001, 1005, 126 Stat. at 1099-1101, 1105 (codified at 21 U.S.C. §§ 356c(e), 826(h)).

⁴⁰Id. §§ 1002, 1006, 126 Stat. at 1102, 1105-06 (codified at 21 U.S.C. §§ 356c-1, 826a).

date list of drugs that it determines to be in shortage, which, subject to public health, trade secret, and confidentiality provisions, must be publicly available.⁴¹ To meet this requirement, FDA posts information about drug shortages on its website, including the name of the drug and the reason for the shortage.

Performance Measures and Internal Controls

Under the Government Performance and Results Act of 1993 (GPRA), as amended by the GPRA Modernization Act of 2010, agencies are statutorily required to prepare annual performance plans that articulate goals for the upcoming fiscal year and must include indicators that the agency will use to measure its performance.⁴² Standards for internal control in the federal government and federal guidance on performance management also call for agencies to establish objectives and performance measures for programs that clearly link to agency-wide goals.⁴³ As our prior work has shown, performance measures are a key tool to help managers assess progress toward the stated agency-wide strategic goals and program-level objectives.⁴⁴ Leading agencies seek to establish clear hierarchies of results-oriented performance measures and targets to ensure that the agency is achieving its mission and strategic goals. Such performance measures help agencies make resource decisions and foster accountability to communicate agency progress to Congress and the public.

Internal control, which is synonymous with management control, comprises the plans, methods, and procedures used to ensure an agency is meeting its missions, goals, and objectives, which supports

⁴¹Id. § 1004, 126 Stat. at 1104-05 (codified at 21 U.S.C. § 356e).

⁴²31 U.S.C. § 1115(b).

⁴³[GAO/AIMD-00-21.3.1](#).

⁴⁴For example, see our findings in GAO, *Managing for Results: Enhancing Agency Use of Performance Information for Management Decision Making*, [GAO-05-927](#) (Washington, D.C.; Sept. 9, 2005); *Results-Oriented Cultures: Creating a Clear Linkage between Individual Performance and Organizational Success*, [GAO-03-488](#) (Washington, D.C.; Mar. 14, 2003); *Agencies' Annual Performance Plans Under the Results Act: An Assessment Guide to Facilitate Congressional Decisionmaking*, [GAO/GGD/AIMD-10.1.18](#) (Washington, D.C.; February 1998); and *Program Performance Measures: Federal Agency Collection and Use of Performance Data*, [GAO/GGD-92-65](#) (Washington, D.C.; May 4, 1992).

performance-based management.⁴⁵ Such controls help agency program managers achieve desired results and provide reasonable assurance that program objectives are being achieved through, among other things, effective and efficient use of agency resources. In addition, internal control standards in the federal government call for agencies to communicate with and obtain information from external stakeholders, compare actual performance to planned or expected results, review performance measures and indicators, compare and assess different sets of data to establish relationships and then take appropriate action, and to document all internal controls, transactions, and other significant events. In addition, we have previously reported on the importance of interagency collaboration.⁴⁶ Collaboration can be broadly defined as any joint activity that is intended to produce more public value than could be produced when organizations act alone.

Shortages of Drugs Containing Controlled Substances Rose Sharply After 2007; Many Involved Generic Pain Relievers and Drugs Manufactured by Few Companies

Shortages of drugs containing controlled substances have increased sharply in recent years; such shortages lasted for nearly a year, on average, and the majority of drugs were in shortage multiple times. Half of the shortages of drugs containing controlled substances identified as critical by UUDIS were analgesics (pain relievers) and most involved generic drugs.

⁴⁵GAO/AIMD-00-21.3.1.

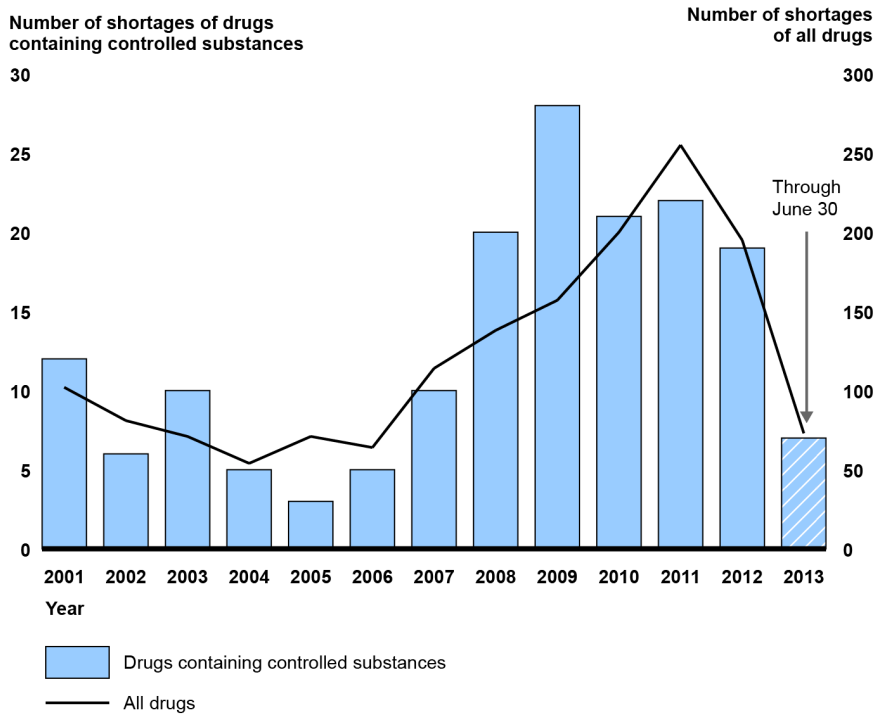
⁴⁶GAO-06-15.

Shortages of Drugs Containing Controlled Substances Have Spiked in Recent Years; Most Were in Shortage Multiple Times and for Nearly 1 Year on Average

Of the 168 shortages of drugs containing controlled substances that were reported from January 2001 through June 2013, nearly 70 percent began between 2008 and 2013.⁴⁷ The number of new shortages reported each year peaked in 2009—with 28 that year—and has somewhat declined since then, though the number still remains significantly above pre-2008 levels. (See fig. 2.) The recent increase in these shortages mimics the pattern we have found for shortages of all drugs, which have also sharply increased since 2007 and subsequently declined after peaking in 2011. The 168 shortages of drugs containing controlled substances represent a small percentage of the total 1,575 drug shortages reported from January 2001 through June 2013.

⁴⁷A shortage is counted in the total for “reported” shortages in the year that UUDIS is first notified of the shortage. For example, a shortage reported in July 2010 and resolved in March 2012 would be counted as a reported shortage in 2010. It would not be counted as a reported shortage in either 2011 or 2012.

Figure 2: New Shortages of Drugs Containing Controlled Substances and All Drugs Reported January 2001 through June 2013, by Year



Source: GAO analysis of University of Utah Drug Information Service data. | GAO-15-202

Note: A shortage is counted as “reported” in the year that the University of Utah Drug Information Service is first notified of the shortage. The totals for shortages of all drugs reported for 2007 through 2011 may differ slightly from what we reported in our 2011 report due to minor modifications by the University of Utah Drug Information Service to its data since that report. See [GAO-12-116](#), 16.

The vast majority of shortages of drugs containing controlled substances—96 percent—lasted longer than 1 month and some of these shortages spanned multiple years. (See table 1.) The average duration was nearly 1 year; however, some were much longer. For instance, a single shortage of lorazepam injection, a medication used to treat anxiety, lasted slightly more than 5 years.

Table 1: Summary of the Duration of Shortages of Drugs Containing Controlled Substances, January 2001 through June 2013

Duration of shortages	Number of shortages	Percent^a	Average duration^a (in days)
Shortages lasting less than 30 days	6	4	17
Shortages lasting between 30 and 365 days	96	61	160
Shortages lasting more than 365 days	55	35	729
Shortages lasting zero days ^a	11	—	—
Total	168	100	354

Source: GAO analysis of University of Utah Drug Information Service data. | GAO-15-202

Note:

^aWe excluded 11 shortages of the 168 shortages of drugs containing controlled substances identified by the University of Utah Drug Information Service from January 2001 through June 2013 from this analysis because these shortages lasted 0 days, leaving 157 shortages. The majority of these excluded shortages represented manufacturers' decisions to discontinue their production of a drug.

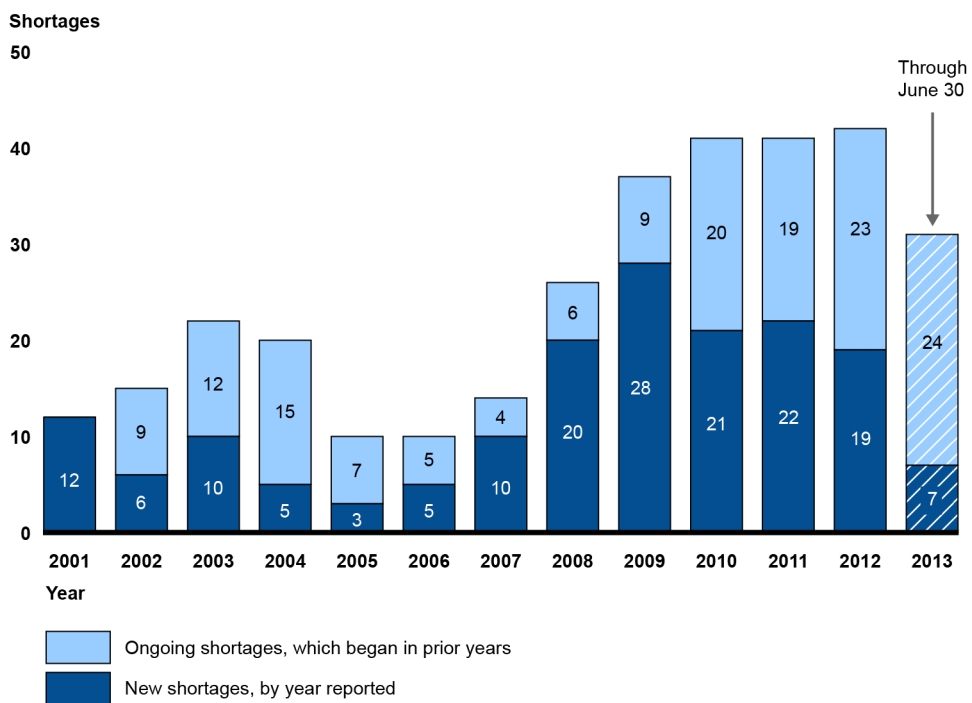
Most shortages—143 of 168—involved drugs that were in short supply multiple times, ranging from two to seven times. Forty-five different drugs containing controlled substances were reported to be in shortage multiple times from January 2001 through June 2013, representing 143 individual shortages. Overall, these 45 different drugs were in short supply for an average of about 3 years. For instance, oxycodone oral solution, a drug that is used to treat moderate to severe pain, was in shortage for the longest combined amount of time over the course of four different shortages, with a combined duration of over 8.5 years.

Drugs containing schedule II substances accounted for more than half of the shortages of drugs containing controlled substances that were reported from January 2001 through June 2013. Fifty-seven percent of shortages involved schedule II substances, while the remaining schedules—schedules III, IV, and V—comprised 15, 26, and 2 percent of shortages, respectively. Shortages of drugs containing schedule II, III, and IV substances ranged on average from 356 days to 359 days. However, shortages of schedule V drugs were shorter, lasting an average of 228 days.

Though the number of shortages reported has declined in recent years, the number of active shortages of drugs containing controlled substances remains high. (See fig. 3.) The active shortage total for each year includes both (1) new shortages reported that year and (2) shortages that started in a prior year that were still ongoing. For example, a shortage reported in July 2010 and resolved in March 2012 would be counted as

an active shortage in three different years (2010, 2011, and 2012). Rather than peaking in 2009, as the number of new shortages reported did, the number of active shortages has remained more or less constant, with 37 to 42 active shortages of drugs containing controlled substances per year from 2009 to 2012. For instance, in 2012, there were 19 new shortages reported that year and another 23 shortages that started in prior years and remained ongoing through some of the year. As of June 2013, there were 31 active shortages of drugs containing controlled substances.

Figure 3: Number of Active Shortages of Drugs Containing Controlled Substances, January 2001 through June 2013, by Year



Source: GAO analysis of University of Utah Drug Information Service data. | GAO-15-202

Note: The active shortage total for each year includes (1) new shortages reported that year and (2) shortages that were reported in a prior year that remained ongoing.

Half of Critical Shortages of Drugs Containing Controlled Substances Were of Pain Relievers and Many Involved Generic Products

Of the 87 shortages of drugs containing controlled substances identified as critical by UUDIS from January 2001 through June 2013, half involved pain relievers (analgesics) (44 of 87). These shortages were identified as critical by UUDIS because alternative medicines were not available, the shortages affected multiple manufacturers, or it received multiple reports of shortages from different provider institutions. There were also shortages of anti-anxiety medications, sedative hypnotic drugs, and stimulants. (See table 2.) All of these types of drugs belong to the broader class of drugs that affect the central nervous system, and are used to treat seizures, manage anxiety, and to provide sedation and pain reduction, among other things.⁴⁸

Table 2: Summary of Critical Shortages of Drugs Containing Controlled Substances by Therapeutic Class, January 2001 through June 2013

Therapeutic class	Number of critical shortages	Percent of critical shortages
Analgesic	44	51
Antianxiety	7	8
Sedative hypnotic	8	9
Stimulant	5	6
Other	23	26
Total	87	100

Source: GAO analysis of University of Utah Drug Information Service and Truven Health Analytics (Red Book). | GAO-15-202

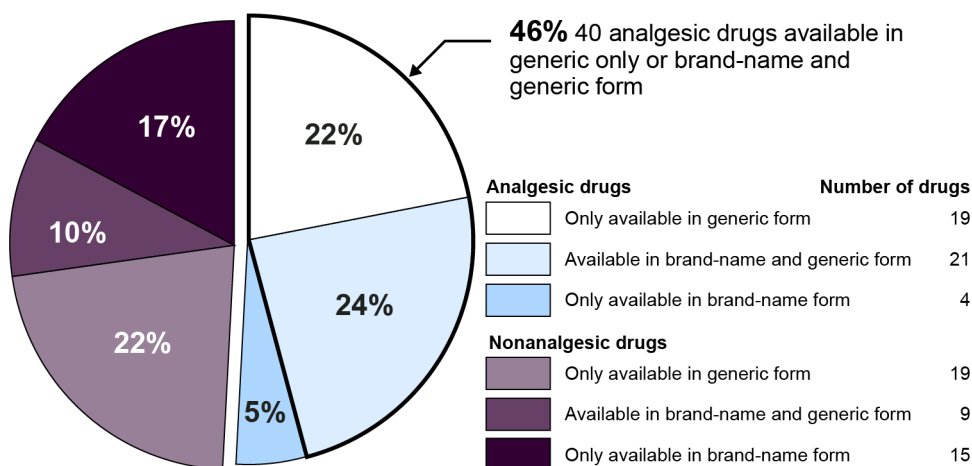
Note: This figure reflects 87 of the 168 (52 percent) shortages of drugs containing controlled substances reported during this time period; it is limited to the shortages the University of Utah Drug Information Service identified as critical. Red Book is a compendium published by Truven Health Analytics that includes information about the characteristics of drug products.

Most critical shortages of drugs containing controlled substances—68 of 87 (78 percent)—involved a generic drug. This 78 percent includes 38 critical shortages of drugs available only in generic form and 30 shortages of drugs available in both brand-name and generic forms. Another 19 critical shortages were of drugs available only in brand-name form (22 percent). Our analysis also showed that 40 critical shortages (46 percent) involved generic pain relievers. These 40 critical shortages include 19 shortages of analgesics only available in generic form

⁴⁸Central nervous system and anesthesia drugs represented the therapeutic class with the highest frequency of all critical drug shortages reported from January 2009 through June 2013. See [GAO-12-116](#) and [GAO-14-194](#).

(22 percent) and 21 shortages of analgesics available in brand-name and generic form (24 percent). (See fig. 4.)

Figure 4: Distribution of Critical Shortages of Drugs Containing Controlled Substances by Therapeutic Class and Product Type, January 2001 through June 2013



Source: GAO analysis of data from the University of Utah Drug Information Service and Truven Health Analytics (Red Book). | GAO-15-202

Note: This figure reflects 87 of the 168 (52 percent) shortages of drugs containing controlled substances reported during this time period; it is limited to the shortages the University of Utah Drug Information Service identified as critical. Non-analgesics include all other therapeutic classes, such as anesthetics and anti-anxiety medications. Red Book is a compendium published by Truven Health Analytics that includes information about the characteristics of drug products.

Most critical shortages of drugs containing controlled substances—79 shortages (91 percent)—involved drugs that were manufactured by four or fewer companies and 39 of those shortages involved drugs manufactured by only one company. The remaining 8 shortages involve drugs that were manufactured by five or more companies (9 percent).

Finally, injectable drugs were in short supply slightly more often than orally administered drugs during this time period, with 44 critical shortages of injectable drugs (51 percent) and 35 critical shortages of orally administered drugs (40 percent). The remaining shortages involved drugs with other routes of administration, such as those administered topically or via the rectum.

Shortages of Drugs Containing Controlled Substances Can Compromise Patient Care and Create Challenges for Providers

According to provider and patient organizations, during shortages of drugs containing controlled substances, patients may receive less effective care, experience medication errors, or not receive treatment at all. Provider organizations also report that providers encounter serious challenges when such drugs are in short supply, requiring them to spend time and resources to mitigate the effects of shortages.

Shortages Can Result in Less Effective Care, Medication Errors, and Delayed or Canceled Treatment

FDA reports that drug shortages can pose a significant threat to the public health by adversely affecting care for patients. According to FDA, drug shortages can delay or deny needed care for patients. Drug shortages can also lead prescribers to use second-line alternatives, which may be less effective or pose additional risks. In addition, provider and patient organizations we spoke with told us that shortages of drugs containing controlled substances have resulted in less effective patient care. For example, representatives from an EMS organization told us that some providers limited the amount of pain medication administered to patients in order to make their supply of the drugs last longer, resulting in patients with unmanaged pain. In addition, some providers often have to use substitutes during shortages that involve undesirable side effects or can be less effective, according to provider organizations.⁴⁹ Representatives from the American Society of Anesthesiologists told us that when providers have to use an alternative anesthesia medication that is not the preferred treatment, patients can experience longer recovery times, delayed awakening, or postoperative nausea or vomiting. Medications can affect patients differently and, as a result, finding an effective substitute during a shortage can be complicated. For instance, according to provider and patient organizations focused on mental health issues, providers treating patients with ADHD may need to try different drugs

⁴⁹An American Society of Anesthesiologists' survey revealed that over 95 percent of its members used an alternative medication because of a shortage and another 50 percent modified a procedure in some way because of a shortage. The survey also showed that the anesthesia drugs with the highest reported frequency of shortage were fentanyl and thiopental, both of which are controlled substances, as well as succinylcholine, propofol, and pancuronium, which are not controlled substances. The American Society of Anesthesiologists, *2012 ASA Drug Shortage Survey Results*, accessed January 20, 2015, <http://asahq.org/advocacy/federal-activities/regulatory-activity/drug-shortages#Drug%20Shortages%20Survey>.

containing other controlled substances and at varied doses to find one that works, although perhaps not as effectively as the patient's usual medication. Even switching from an extended-release formulation to an immediate-release formulation of the same drug can have a significant effect on a child with ADHD if the child's school does not have a nurse to supervise the child taking medication during the day, according to the director of UUDIS. One organization representing patients and families affected by this disorder, Children and Adults with Attention Deficit/Hyperactivity Disorder, found that 18 percent of survey respondents had to change medications during a shortage of ADHD medications. Patients may also be seriously affected by changing to a different route of administration of the same drug during shortages. Patients receiving hospice care or near the end of life may require injections because they cannot swallow a pill for example. Therefore, during a shortage of a morphine injection, clinicians may have to switch the patient to another injectable pain reliever because the patient cannot swallow the morphine tablet, according to the director of UUDIS.

Patients are at increased risk of experiencing medication errors during these shortages. Providers may have to use drugs in unfamiliar dosages or concentrations during shortages of drugs containing controlled substances, which can increase the risk of medication errors and lead to serious consequences for patients. For instance, in its survey of health care practitioners, the Institute for Safe Medication Practices found several instances of overdose and death from providers incorrectly converting doses for pain relievers during a morphine shortage.⁵⁰ Errors administering sedatives have also led to patients receiving too much or too little medication, resulting in unintended consciousness during surgery, agitation, and increased recovery times. EMS organizations also noted that the providers they represent are particularly at risk for administering medication incorrectly as they typically have less experience dealing with different medications, doses, or concentrations than hospital-based providers. Additionally, representatives of an EMS organization added that EMS providers deliver care in a mobile environment, which further increases the risk of administering medication incorrectly.

⁵⁰Institute for Safe Medication Practices, *Drug Shortages: National Survey Reveals High Level of Frustration, Low Level of Safety*, accessed October 1, 2012, <http://www.ismp.org/newsletters/acutecare/articles/20100923.asp>.

Patients may have to delay or forgo care because of shortages of drugs containing controlled substances. For instance, provider organizations told us that providers have had to cancel or delay surgeries and procedures during shortages of anesthesia drugs. EMS associations we spoke with also reported that patients were at risk when drugs that are used to treat seizures were in short supply and there were no available substitutes.

In addition to compromised care, patients faced other hardships. For example, parents spent significant time tracking down ADHD medications that were in shortage for their children, according to provider and patient organizations focused on mental health issues, such as Children and Adults with Attention Deficit/Hyperactivity Disorder and the American Academy of Child and Adolescent Psychiatry. In particular, these organizations reported that some parents of children with ADHD called more than 30 pharmacies to find their children's medication. Representatives of mental health organizations also reported that patients faced increased costs during shortages. Some paid higher prices for their drugs when generic ADHD medications were in short supply and only the more expensive brand-name drug was available. In other instances, patients found they had to visit their physicians more often to obtain new prescriptions when pharmacies with dwindling supplies could only partially fill their orders, which then resulted in additional fees from the physician to obtain a new prescription, according to mental health organizations.⁵¹

⁵¹The CSA precludes prescriptions for such schedule II ADHD medications from being refilled, so, according to mental health organizations, patients needed to see their physician more frequently when they were not able to get their prescriptions filled completely. The CSA establishes various requirements that govern prescriptions of controlled substances depending upon the schedule of the drug. For example, schedule II substances, including amphetamine used to treat ADHD, cannot be dispensed without a written prescription of a practitioner, except in emergency situations, and cannot be refilled. 21 U.S.C. § 829(a). Schedule III and IV substances require a prescription; however, the prescription can be filled or refilled for up to 6 months after the date of the prescription and refilled up to five times. 21 U.S.C. § 829(b).

Providers Face Challenges Mitigating the Effects of Shortages of Drugs Containing Controlled Substances

FDA reports and provider organizations told us that shortages of drugs containing controlled substances burden providers, as the providers must spend time and resources addressing such shortages rather than providing care to patients. For example, some providers have had to add full-time staff to manage the effects of shortages and track down medications, according to provider organizations. Officials from a provider organization said that those who could not afford the cost of additional personnel may have had to divert staff from patient care. EMS organizations said that shortages can be particularly challenging for EMS organizations that typically have fewer staff or resources than large hospitals to dedicate to finding drugs that are in short supply. These reports corroborate research on the cost of all drug shortages; researchers at the University of Michigan, in collaboration with the American Society of Health-System Pharmacists, found that the labor costs for managing all drug shortages for U.S. hospitals is approximately \$216 million annually.⁵²

In trying to mitigate the effects of shortages of drugs containing controlled substances, providers may face situations that pose safety and efficacy concerns, and create ethical dilemmas. For example, providers may opt to turn to expired medications. FDA states that expired medications can be less effective or pose risks due to a change in chemical composition or decrease in potency. In limited cases FDA has exercised enforcement discretion to enable use of expired drugs to alleviate the effect of a shortage. Some states allow the use of expired drugs and providers in those states often pay for expensive tests to assess an expired drug's stability and efficacy, according to provider organizations.⁵³ Obtaining drugs containing controlled substances in short supply through compounding pharmacies is another avenue providers may take that can pose risks to patients and can cost significantly more than noncompounded drugs.⁵⁴ Compounded drugs can raise safety and

⁵²R. Kaakeh, B.V. Sweet, C. Reilly, et al., "Impact of Drug Shortages on U.S. Health Systems," *American Journal of Health-System Pharmacy*, vol. 68, no. 19 (2011). This estimate is based on the number of shortages in 2010, when the number of shortages of all drugs was about half of what it was in 2013, according to data from UUDIS.

⁵³For instance, in July 2013, Pennsylvania's Bureau of Emergency Medical Services instituted a procedure to allow EMS providers to apply for an exemption that allows them to use certain drugs for 6 months beyond the drugs' expiration date.

⁵⁴Drug compounding is the process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a drug tailored to the needs of an individual patient.

efficacy concerns because the pharmacies that produce such drugs may be exempt from some FDA requirements that apply to drug manufacturers.⁵⁵ Provider organizations also said drugs containing controlled substances from compounding pharmacies are significantly more expensive than traditional suppliers and have a shorter shelf life, which can result in wasted product.

EMS providers may face additional challenges during shortages of drugs containing controlled substances, compared to other providers. EMS organizations said that their providers typically obtain medications either through contracts with hospitals or directly from distributors. However, provider organizations said that during periods of short supply, it may be a low priority for hospitals to ensure that EMS providers receive drugs in shortage because hospitals will typically fill their own supply first. EMS organizations added that distributors are more likely to cater to hospitals and other, larger providers because EMS providers are comparatively small purchasers.⁵⁶ Additionally, EMS organizations reported some confusion about whether the providers they represent can transfer medications to other affiliated EMS providers because of federal and

⁵⁵Drugs compounded by a licensed pharmacist in a state licensed pharmacy or federal facility, or by a licensed physician, and that meet the conditions of section 503A of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 353a, can qualify for exemptions from the FDA approval requirements, the requirement to label products with adequate directions for use, and the requirement to comply with current good manufacturing practice requirements. The exemptions in section 503A are only available if the licensed pharmacist or licensed physician obtains a valid prescription for an identified individual patient among other things.

Although drug compounding is a traditional component of the practice of pharmacy, concerns have been raised by FDA and others that some pharmacies were going beyond traditional drug compounding for individual patients by producing large quantities of compounded drugs. The Drug Quality and Security Act created a new section 503B of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 353b, under which a compounder can register as an “outsourcing facility.” Drugs compounded in an outsourcing facility by or under the direct supervision of a licensed pharmacist, and that meet the conditions in section 503B of the Federal Food, Drug, and Cosmetic Act, can qualify for exemptions from the FDA drug approval requirements and the requirement to label products with adequate directions for use. Such outsourcing facilities remain subject to current good manufacturing practice requirements.

⁵⁶The drug distributors we spoke with told us that during a shortage they generally use an allocation system in which customers receive a percentage of past orders, in order to ensure equitable distribution among their customers. However, one distributor said that customers who buy more drugs may receive a higher percentage of their order than other customers though all customers would be limited in the quantities that they receive.

state laws.⁵⁷ In addition, the vast majority of EMS providers are governed by state or local clinical protocols and, in some cases, medication formularies designate the specific doses and concentrations of medications that are permitted for use.⁵⁸ As a result, EMS providers in those states and localities are likely to continue to grapple with short supplies, unless state laws or regulations enable them to use different medications, doses, or concentrations than what is allowed under existing formularies or protocols.

DEA Has Not Effectively Administered the Quota Process Due to Missed Time Frames and Weak Internal Controls

DEA did not meet its required time frames for establishing quotas for classes of schedule II substances, and manufacturers report that the lack of timeliness has caused or exacerbated shortages of some of their drugs containing controlled substances. Additionally, our work shows that DEA's lack of internal controls, such as controls to ensure data reliability, performance measures, and monitoring of performance, may hinder the agency's ability to ensure an adequate and uninterrupted supply of controlled substances.

⁵⁷EMS providers must comply with federal laws when handling controlled substances, and may also have to comply with a variety of additional state and local requirements. EMS provider organizations reported confusion among EMS agencies about how to comply with federal requirements related to controlled substances. As a result, officials from the Federal Interagency Committee on EMS said they are working with DEA to clarify DEA regulations and guidance that apply to EMS agencies.

⁵⁸Most EMS providers are required to follow certain protocols that govern how they administer care and, in some cases, adhere to medication formularies, both of which can limit the medications used by these providers. State and local governments regulate the practice of EMS by licensing EMS providers and establishing standards of care, including what medications can be administered by EMS providers. According to the 2011 National EMS Assessment, prepared for the Federal Interagency Committee on Emergency Medical Services, 48 states have either state or locally developed patient care protocols for EMS providers (2 states did not provide information). Additionally, 25 states have medication lists or formularies for EMS professionals, according to this assessment.

DEA Did Not Meet Required Time Frames for Establishing Quotas for Schedule II Substances; Manufacturers Reported Quotas Caused or Exacerbated Shortages of Some of Their Products

Our examination of DEA's Federal Register notices proposing and establishing APQs found that DEA has not met its required time frames for more than a decade. Specifically, DEA has not met the time frames provided in its regulations for proposing APQs for classes of schedule II substances and establishing annual bulk manufacturing and procurement quotas for individual manufacturers since at least 2001.

- Proposing APQs: DEA did not propose APQs in the Federal Register on or before May 1st, as required by DEA's regulations, for any year from 2001 through 2014.⁵⁹ On average, DEA proposed APQs about 5 months after the May 1 deadline specified in its regulations. Additionally, though there is no requirement for when DEA must establish the APQ in the Federal Register, for 10 of the 14 years from 2001 through 2014, DEA established APQs in the Federal Register in December of the application year, generally in the last two weeks of the year.⁶⁰ For one year (2005), DEA established the APQs in the Federal Register in January of the production year. DEA does not inform manufacturers of their quota authorizations until after APQs have been established for the production year; therefore, the date the APQ is established affects when manufacturers receive their quotas.
- Establishing annual bulk manufacturing and procurement quotas: According to our analysis of Federal Register notices, DEA did not meet the requirements specified in the agency's regulations for establishing bulk manufacturing and procurement quotas by July 1, for any year from 2001 through 2014.⁶¹ From our analysis of a random probability sample of YERS/QMS source documents, we estimate that DEA took an average of 182 days in 2011 and 178 in 2012 beyond July 1 to establish annual bulk manufacturing and procurement

⁵⁹21 C.F.R. § 1303.11. The CSA does not designate when DEA is to propose or establish APQs.

⁶⁰We define "application year" as the year in which manufacturers apply for annual quota for the next calendar year. We define "production year" to be the year in which manufacturers can use their quota.

⁶¹21 C.F.R. §§ 1303.12 and 1303.21.

quotas.⁶² In addition to not meeting the time frames in DEA's regulations, our analysis of Federal Register notices found that neither did DEA meet the CSA requirement for establishing bulk manufacturing quotas by October 1 from 2001 through 2013, though it did meet this deadline recently.⁶³ For 2014 annual bulk manufacturing quotas, DEA established manufacturers' bulk manufacturing quotas in September 2013.

Moreover, manufacturers have expressed concerns about DEA's timeliness in establishing quotas and have asserted that the amount of time it takes DEA to respond to their quota applications has contributed to shortages of some drugs containing controlled substances. We obtained FDA data on the manufacturer-reported causes of 40 shortages of drugs containing schedule II controlled substances from January 2010 through June 2013.⁶⁴ These data show that 10 manufacturers reported to FDA that 7 of the 40 shortages of drugs containing schedule II substances during this time period were caused by problems related to quota.⁶⁵ The remaining 33 shortages of drugs containing schedule II substances were caused by other factors, such as manufacturing delays, capacity issues, and product quality issues, according to information reported to FDA by manufacturers.⁶⁶ After reviewing this information, we contacted representatives from all of these companies. Many told us that DEA's lack

⁶²All percentage estimates from the sample of source documents have margins of error at the 95 percent confidence level of plus or minus 10 percentage points or less, unless otherwise noted. All numerical estimates other than percentages have margins of error of plus or minus 10 percent or less of the value of those numerical estimates, unless otherwise noted. Our sample of YERS/QMS source documents includes the entire population of applications submitted by manufacturers that reported shortages caused by quota to FDA and a probability sample of all other applications within each year (2011 and 2012).

⁶³21 U.S.C. § 826(c).

⁶⁴The FDA data reflect information reported by manufacturers to FDA that is subsequently analyzed and categorized by the agency.

⁶⁵These 7 shortages were of drugs that included the substance classes of amphetamine, methylphenidate, or oxycodone, and began in either 2010 or 2011. According to FDA's data, there were several instances of shortages of drugs containing each of these substances between January 2010 and June 2013 and some, but not all, were reportedly caused by quotas.

⁶⁶We previously reported that these are the same factors that cause shortages of drugs generally. See [GAO-14-194](#) for more information on the reasons for shortages of all drugs.

of timeliness in establishing manufacturers' quotas has caused or exacerbated shortages of their products containing schedule II substances. In particular, the representatives said that DEA's timing of establishing annual bulk manufacturing and procurement quotas, which has generally been in late December of the application year, after it establishes the APQ, does not provide manufacturers with enough time to plan for production and order the raw material or API needed to start manufacturing their products at the beginning of the production year in January. Representatives from dosage form manufacturers report that these late decisions leave manufacturers operating solely with what is left in their inventory for the first few months of the production year, which may be limited because manufacturers operate in a lean manufacturing environment where they carry as little inventory as possible.

Additionally, manufacturer representatives said that DEA's lack of timeliness in responding to supplemental quota applications submitted during the production year has also caused or exacerbated shortages of their products. Based on our analysis of a probability sample of YERS/QMS source documents, we estimate that it took DEA an average of 58 days to respond to supplemental quota applications in 2011 and 2012. Within the source documents we reviewed, DEA's fastest response to a supplemental application was 7 days and its longest response took about 5 months. While there are no required time frames for DEA to respond to supplemental applications in the CSA or DEA's regulations, as of July 2012, FDASIA has required DEA to respond to manufacturers' quota requests that relate to shortages caused by quotas within 30 days.⁶⁷ Although this 30-day time frame was not yet a requirement in 2011 and much of 2012, it is worth noting that it often took longer for DEA to respond, suggesting this requirement could pose a challenge during a future shortage. We estimate that DEA responded within 30 days to 21 percent of supplemental applications in 2011 and 2012. Furthermore, we found that DEA took 10 days longer, on average, to respond to supplemental quota applications submitted by manufacturers that reported shortages caused by quota to FDA in 2011, the year in which these shortages began, than other supplemental applications (see table 3). In 2012, however, we found no statistical difference between the estimated amount of time DEA took to respond to both groups of supplemental applications.

⁶⁷Pub. L. No. 112-144, § 1005, 126 Stat. at 1105 (codified at 21 U.S.C. § 826(h)).

Table 3: The Drug Enforcement Administration’s (DEA) Estimated Response Times for Supplemental Applications in Year-End Reporting and Quota Management System (YERS/QMS) Source Documents, 2011 and 2012

YERS/QMS source documents	Applications submitted by manufacturers who reported shortages caused by quota (Y/N)	Average number of days
2011	Y	73
	N	63 ^a
2012	Y	51
	N	54 ^b
Both years	Y	59
	N	58 ^c

Source: GAO analysis of YERS/QMS source documents. | GAO-15-202

Notes: This table reflects our review of a stratified probability sample of 440 source documents from YERS/QMS. This sample included all of the 146 records in 2011 and 2012 that are associated with drug shortages manufacturers reported to the Food and Drug Administration (FDA) were caused by quotas. We consider YERS/QMS records to be associated with these shortages if the record contains a quota application that was (a) submitted by a manufacturer who reported quota caused a shortage of their product to FDA; (b) for a substance that was used in the products reportedly in shortage because of quota; and (c) was submitted during the time of the reported shortage caused by quota. Manufacturers may or may not have reported to DEA that their quota application was related to a shortage. We also analyzed a random sample of 294 records stratified by year that were not associated with any drug shortages reportedly caused by quotas—180 and 114 records from 2011 and 2012, respectively.

^aThe margin of error at the 95 percent confidence level for supplemental applications submitted by manufacturers who did not report shortages caused by quota in 2011 is plus or minus 10.9 percent.

^bThe margin of error at the 95 percent confidence level for supplemental applications submitted by manufacturers who did not report shortages caused by quota in 2012 is plus or minus 13.7 percent.

^cThe margin of error at the 95 percent confidence level for supplemental applications submitted by manufacturers who did not report shortages caused by quota in 2011 and 2012 combined is plus or minus 8.8 percent.

DEA officials acknowledged that the agency has not met the time frames for proposing and establishing quotas, as required by the agency’s regulations. DEA officials cited inadequate staffing of the Quota Unit as the reason why DEA has not met its requirements for proposing APQs and establishing manufacturers’ bulk manufacturing and procurement quotas for schedule II substances. In particular, DEA officials noted that the agency’s workload with respect to quotas has increased substantially and that drug manufacturing has become more complex since the CSA was enacted and DEA’s regulations were established in the 1970s. For example, DEA officials said that when the CSA was enacted and DEA’s regulations were initially established, dozens of companies applied for quota each year, whereas now hundreds of companies apply for quota. Additionally, DEA reports that manufacturers submit substantially more

applications to DEA than they have in the past. In 2012, for example, DEA received over 3,000 quota applications, and officials said that each application necessitates its own evaluation and analysis for each substance as it relates to the application. In addition to an increasing workload, DEA officials said that the agency has faced hiring challenges. In particular, it has been unable to hire additional qualified scientists for the Quota Unit because DEA has not found candidates with the right skills who are also able to pass the background checks required for employment. They also said that offers to qualified candidates have been declined. DEA officials noted that as of October 2014, the agency was still in the process of trying to hire two additional scientific staff for the Quota Unit, which would increase the staffing level to 12 (8 quota scientists and 4 administrative staff).

DEA officials added that the quality and timeliness of manufacturers' quota applications affects DEA's ability to meet its required time frames for proposing APQs and establishing manufacturers' quotas. For example, DEA estimates that the agency follows up with manufacturers on about half of the quota applications to get clarification on the information provided or to obtain additional information. DEA officials said that manufacturers also continue to revise their annual applications as manufacturing conditions change throughout the year, such as when manufacturers gain or lose business or encounter a manufacturing problem that destroys part of their inventory of controlled substances and they seek to replace what was lost.⁶⁸ From our analysis of a probability sample of YERS/QMS source documents, we estimate that although 80 percent of annual applications in 2011 and 65 percent of annual applications in 2012 were submitted in the first two quarters of the application year, another 19 percent of annual applications in 2011 and 22 percent of annual applications in 2012 were submitted in the fourth quarter of the application year. This may represent the first annual application submitted by a manufacturer for the production year or subsequent revisions because YERS/QMS contains both the first annual application submitted and subsequent revisions. DEA officials said that they do not consider manufacturers to be noncompliant with their time frames when they submit annual quota applications after the deadlines. They said they recognize that it is important for manufacturers to submit

⁶⁸DEA's regulations authorize manufacturers to apply for revisions to their quotas at any point. 21 C.F.R. §§ 1303.12(d) and 1303.25(a).

revisions as conditions change, to ensure they receive appropriate amounts of quota. Our review of a sample of YERS/QMS source documents shows that manufacturers often submit annual bulk manufacturing and procurement quota applications throughout the year. Despite this, DEA officials said that they expect the agency will be compliant with its CSA time frames in the future. DEA officials said that moving to an electronic data system for the quota process—YERS/QMS—has helped the agency to be more compliant with its time frames, as well as the reorganization of staff into a separate Quota Unit in 2011.⁶⁹ They noted that the agency has already made progress in meeting its CSA-required time frames for establishing annual bulk manufacturing quotas in 2014.

Although DEA acknowledges it has generally not adhered to the quota setting time frames required by the CSA and the agency's regulations in the last 14 years, agency officials do not agree that quotas can cause shortages of drugs containing schedule II substances. In particular, according to DEA, shortages cannot be related to quotas established by the agency because DEA authorizes quotas at the basic class level for a substance—such as amphetamine or morphine. DEA cannot authorize quota for specific drug products containing those substances, as this is precluded by the CSA. DEA officials said the agency has no control over what specific drug products manufacturers actually produce with the quota authorized. For example, if DEA authorized 10,000 grams of morphine to a manufacturer, the manufacturer—and not DEA—then decides how to authorize the quota amongst its various products that contain different formulations, dosage forms, and concentrations.

We cannot confirm whether DEA's lack of timeliness in establishing annual and supplemental quotas has caused or exacerbated shortages. However, by not responding to annual applications in accordance with the time frames required by its regulations or the CSA and by not acting promptly on supplemental applications, DEA may hinder manufacturers' ability to manufacture drugs that contain schedule II controlled substances that may help prevent or resolve a shortage.

⁶⁹DEA officials report that this change is provisional as it is pending finalization.

DEA's Weak Internal Controls Jeopardize Its Ability to Effectively Manage the Quota Process and Ensure an Adequate Supply of Controlled Substances for Legitimate Medical Use

DEA does not have sufficient internal controls to effectively oversee and manage the quota process and therefore may not be able to appropriately respond to quota applications related to shortages when they arise. In particular, DEA does not have adequate controls to ensure the reliability of the YERS/QMS system that it uses to track manufacturers' quota applications and record its quota decisions. DEA officials told us there are no systematic quality checks to ensure that the data in YERS/QMS are accurate, such as electronic checks for data outliers or manual comparisons of YERS/QMS data to source documents (i.e., manufacturers' quota applications and corresponding DEA decision letters) to identify inconsistent information. Instead, DEA officials said that when manufacturers submit their quota applications electronically, YERS/QMS automatically checks to ensure that the manufacturer applying for quota has a valid DEA registration. Additionally, DEA officials said they added an electronic prompt to YERS/QMS that asks manufacturers to reexamine and confirm quota requests that are for smaller amounts than they have already received for the production year. Officials told us that the Quota Unit also reviews the information submitted by manufacturers and will contact them when information entered looks inconsistent or out of the ordinary. DEA also reports that managers verify that the information entered into YERS/QMS by the Quota Unit is accurate. Though DEA takes some steps to ensure the accuracy of its YERS/QMS data, the agency has not systematically checked to make sure that its efforts are sufficient or having the intended effect. Lacking systematic data checks is inconsistent with federal standards for internal control, which calls for agencies to have appropriate control activities in place, such as periodic data checks, to ensure that the data used by the agency for decision making are accurate.⁷⁰ Without controls in place to ensure the accuracy of YERS/QMS data, DEA cannot provide reasonable assurance that it has correct information in its official record of the dates and amounts of its quota decisions beyond the individual electronic and hard copies of decision letters it keeps for retention purposes. Further, inaccuracies in YERS/QMS data will also affect the accuracy of future quota applications submitted by manufacturers, as YERS/QMS automatically populates information on quotas previously authorized by DEA from the prior 2 years into a new quota application.

⁷⁰[GAO/AIMD-00-21.3.1.](#)

In our review of YERS/QMS data from 2011 and 2012, we found a large number of errors in 2011 and a significant reduction in the number of errors in 2012. Based on our analysis of a probability sample of YERS/QMS data, we estimate that 44 percent of the records in 2011 and 10 percent of the records in 2012, each of which corresponds to one quota application and DEA decision letter, contained at least one data field with incorrect data, such as incorrect dates or amounts of quota requested or authorized.⁷¹ In particular, we estimate that errors in the quota application fields declined substantially in 2012, with, for example, errors in the total amount of quota requested field dropping from 13 percent of records in 2011 to 3 percent of records in 2012. See table 4 for the specific fields in which we found errors in our review for years 2011 and 2012.

⁷¹This difference is significant with a margin of error at the 95 percent confidence level of plus or minus 10 percentage points.

Table 4: Estimated Percent of Errors in the Drug Enforcement Administration’s (DEA) Year-End Reporting and Quota Management System (YERS/QMS)

	Estimated percent of records with errors ^a	
Data fields	2011	2012
Quota application		
Application year	0%	0%
Company name	1%	0%
Substance name	0%	1%
Quota type	1%	0%
Date submitted	23%	1%
Total amount of quota	13%	3%
Decision letter		
Application year	0%	0%
Company name	1%	0%
Substance name	1%	0%
Quota type	1%	0%
Date mailed	9%	3%
Total amount of quota	5%	2%
Total	44%^b	10%^b

Source: GAO analysis of YERS/QMS data and source documents obtained from DEA. | GAO-15-202

Notes: This table reflects our review of a stratified random sample of 440 source records from YERS/QMS. The sample included all of the 146 records in 2011 and 2012 that are associated with drug shortages manufacturers reported to the Food and Drug Administration (FDA) were caused by quotas. We consider YERS/QMS records to be associated with these shortages if the record contains a quota application that was (a) submitted by a manufacturer who reported quota caused a shortage of their product to FDA; (b) for a substance that was used in the products reportedly in shortage because of quota; and (c) was submitted during the time of the reported shortage caused by quota. Manufacturers may or may not have reported to DEA that their quota application was related to a shortage. We also analyzed a random sample of 294 records stratified by year that were not associated with any drug shortages reportedly caused by quotas—180 and 114 records from 2011 and 2012, respectively.

^aAll percentage estimates have margins of error at the 95 percent confidence level of plus or minus 10 percentage points or less.

^bRows may not sum to total because some records have errors in more than one data field. Therefore, such records are counted towards the total number of errors for multiple data fields but count only once for the total number of records with any error.

DEA officials said 2011 was a transitional year for YERS/QMS as manufacturers first started submitting quota applications electronically, and they expected the information for 2012 and beyond to be more accurate. DEA officials noted that they consider the information submitted to YERS/QMS by manufacturers to belong to the manufacturers and therefore DEA officials do not correct this information, even when they learn that it is not accurate. Instead, DEA officials said that they ask

manufacturers to submit a revised application and they mark the original application as withdrawn, as well as make a note in YERS/QMS that the application will be corrected by manufacturers. Nonetheless, we removed applications marked as withdrawn from our analysis and we still found errors in the YERS/QMS data for manufacturers' quota applications, as well as in the data for DEA's quota decisions. As YERS/QMS data is the official record of how much quota is requested by manufacturers and authorized by DEA, maintaining accurate records is important for the management of the quota setting process.

DEA also does not have agency-wide performance measures related to establishing quotas or ensuring an adequate and uninterrupted supply of controlled substances to assess how well the program is carrying out its responsibilities.⁷² Federal internal control standards state that performance measures are an important management tool and that such measures provide critical information to managers about agency performance and program outcomes.⁷³ Such performance information can demonstrate progress toward goals and help program managers determine how to allocate resources among competing priorities. DEA officials said that performance measures related to establishing quotas or ensuring an adequate and uninterrupted supply of controlled substances would be inappropriate because of the complexity of individual quota applications and the difficulty of projecting the number of quota applications for future years. Nonetheless, performance measures related to quotas—such as the percentage of applications that require follow-up by DEA because of missing documentation—are a critical internal control, without which DEA cannot determine if its process for establishing quotas is having the desired outcome of ensuring an adequate and uninterrupted

⁷²DEA does have agency-wide performance measures to assess its performance of reducing the diversion of licit drugs, such as the number of scheduled investigations completed each year. We have previously reported on these measures and recommended that DEA reassess its set of performance measures for the Diversion Control Program to identify ways to enhance the measures' link to the outcome of reducing diversion. See GAO, *Prescription Drug Control: DEA Has Enhanced Efforts to Combat Diversion, but Could Better Assess and Report Program Results*, [GAO-11-744](#) (Washington, D.C.: Aug. 26, 2011).

⁷³*Standards for Internal Control for the Federal Government* state that the establishment and review of performance measures and indicators is a control activity and that monitoring internal controls allows agencies to assess the quality of performance over time. See [GAO/AIMD-00-21.3.1](#), 14, 20. We have also reported on the importance of establishing performance measures that demonstrate how well a program is achieving its goals. See [GAO/GGD-96-118](#).

supply of controlled substances for legitimate medical use. In the absence of such performance measures, DEA is missing important information for program managers to use when making decisions about program resources and the agency cannot effectively demonstrate program results.

In addition, DEA officials told us that they do not monitor or analyze available data from YERS/QMS to assess its administration of the quota process, which federal standards for internal control state is an important component of managing a program.⁷⁴ DEA officials said that the agency does not monitor or analyze these data and that they do not use YERS/QMS to produce aggregate information on timeliness or other performance metrics and the agency has no plans to do so as of October 2014. Absent such analysis, DEA is unable to evaluate its responses to manufacturers' quota applications or to understand the nature of its workload. For example, whereas DEA previously withheld some of the amphetamine APQ to authorize later in the year, officials told us that the agency initially granted more of the amphetamine APQ in 2012 to manufacturers than it had previously, to see if manufacturers would still claim that there was a shortage of their products. However, DEA officials said they did not monitor the effect of this decision, which they said was unprecedented, and they were therefore unsure if it had an effect on shortages or the agency's workload. Officials were unable to say if this change resulted in manufacturers submitting fewer supplemental applications for amphetamine that year. Additionally, DEA officials cited manufacturers' incomplete applications and frequent revisions as affecting the agency's ability to meet its required time frames. However without monitoring or analyzing data to identify how frequently manufacturers submit incomplete and revised applications, DEA lacks information to assess the effect on the agency's workload. This lack of monitoring also prevents DEA from determining whether a few manufacturers are repeatedly submitting incomplete applications or if there is a larger, systemic issue to address. DEA therefore cannot identify appropriate means to help prevent such issues in the future, such as through in-depth training or guidance.

⁷⁴*Standards for Internal Control for the Federal Government* state that managers need to compare actual performance to planned or expected results throughout the organization and analyze significant differences. See [GAO/AIMD-00-21.3.1](#), 13.

Finally, DEA officials told us that the agency does not have protocols, policies, or other documentation to manage how the agency processes quota applications and establishes APQs and annual and supplemental quotas for individual manufacturers.⁷⁵ Instead, DEA officials told us that the agency exclusively relies on its regulations and the CSA to serve as guidance on how to conduct these activities. According to federal internal control standards, agencies should have written documentation, such as detailed policies, procedures, and practices, to fit their agency's operations and to ensure that they are built into, and an integral part of, operations. The absence of written guidance may also pose a risk to the consistency of DEA's future operations in the event of staff turnover, changes in administration, or any other disruption that could lead to a loss of institutional knowledge.⁷⁶

The need for detailed policies, procedures, and practices is particularly important because the activities conducted by Quota Unit staff are very complex, requiring staff to weigh data from at least five different sources and to make recommendations about how to authorize the APQ among various manufacturers. Having additional guidance for these activities is key to help ensure that staff in the Quota Unit process applications consistently and that they are adhering to DEA's regulations and the CSA when setting quotas. For instance, Quota Unit staff analyze and reconcile data from multiple sources in order to recommend quotas that meet estimated legitimate medical need. One such data source is ARCOS, DEA's system for tracking the distribution of controlled substances, which DEA uses in determining how much quota to authorize. Officials told us that there are many instances in which ARCOS data are unreliable and therefore it may contradict information from other sources used by quota scientists, such as the sales information manufacturers provide in their

⁷⁵*Standards for Internal Control for the Federal Government* state that all internal controls, transactions, and other significant events need to be clearly documented, and the documentation should be readily available for examination. The documentation should appear in management directives, administrative policies, or operating manuals and may be in paper or electronic form. See [GAO/AIMD-00-21.3.1](#), 15.

⁷⁶We have previously reported on the risk to the management and operational continuity at agencies due to a lack of written policies and procedures. See, for example, GAO, *Social Security Disability: Management Controls Needed to Strengthen Demonstration Projects*, [GAO-08-1053](#) (Washington, D.C.: Sept. 26, 2008).

quota applications.⁷⁷ Although quota scientists may be faced with contradictory information, it is left to the discretion of the Quota Unit staff to determine how to reconcile conflicting data sources, as there are no written policies or guidance and this level of detail is not included in DEA's regulations or the CSA. Moreover, DEA officials told us that the reliability of different data sources can vary based on the substance and the quota applicant. They noted that in some cases, manufacturer-reported sales data may not be as reliable as data on the number of retail prescriptions dispensed, whereas for a different substance or quota applicant, the reverse may be true. Nonetheless, despite the need to consider data sources differently relative to the substance class or quota applicant, there is nothing in the CSA or DEA's regulations about how to do this and DEA has no additional guidance on the matter.

Additionally, when asked how they train new staff if there is no written guidance about the quota process, DEA officials said that they train new Quota Unit staff about the CSA and DEA's regulations through on-the-job training and using presentations created for industry. There are no specific documents developed for the exclusive purposes of training new staff. DEA officials said that the presentations for industry give new Quota Unit staff an overview of the quota process and that everything else must come from on-the-job training, as each function within the Quota Unit is unique and each quota application is different from the next. DEA officials told us that they ensure consistency in their decision-making by having the Deputy Assistant Administrator of the Office of Diversion Control review and authorize every quota decision that is made. However, given the volume of quota applications that DEA processes each year—over 3,000 in 2012—it is unreasonable to expect that the Quota Unit staff can make consistent decisions with no written guidance. Similarly it is not reasonable to assume that one senior manager can devote sufficient time to review these many staff decisions and ensure that quotas are set in accordance with DEA's regulations and the CSA. Further, the lack of written guidance poses a risk to the continuity of the agency's operations should personnel leave or be reassigned.

⁷⁷In the course of our work, DEA officials told us that ARCOS data were unreliable unless verified by DEA officials against source documents located at registrants' place of business.

DEA and FDA Have Not Established a Sufficiently Collaborative Relationship, Which Could Hinder Their Abilities to Effectively Coordinate and Address Future Shortages

FDASIA contains provisions that require DEA and FDA to coordinate their activities where additional quota may be needed to address a shortage of a drug containing controlled substances, though no such opportunity has occurred since the law's enactment in 2012. In addition, FDASIA requires each agency to report to Congress annually describing the coordination between the two agencies on efforts to prevent or alleviate shortages. Although both agencies report that their working relationship has improved in recent years—namely by establishing a point of contact at DEA who is responsible for coordinating with FDA's DSS—the agencies' use of essential collaborative practices to enhance their abilities to successfully coordinate to resolve or mitigate shortages has been limited.⁷⁸ We have previously identified key practices that agencies need for enhanced and sustained collaboration, including defining and articulating a common outcome and establishing compatible policies, procedures, and other means to operate across agency boundaries.⁷⁹ Running throughout these practices are a number of factors, such as trust, that are important elements for a collaborative working relationship.

One barrier to effective coordination between the two agencies is that DEA and FDA have not defined and articulated a common outcome related to shortages of drugs containing controlled substances. FDASIA gives FDA the authority to create and maintain a list of drug shortages.⁸⁰ However, the two agencies sometimes disagree about whether a shortage exists. This is a fundamental concern because FDASIA also contains provisions that require the two agencies to work together to address shortages of drugs subject to quotas. According to DEA, FDA has posted shortages on its website when, from DEA's perspective, there is no shortage. DEA often views drugs containing the same substance class as viable substitutes for one another, even when the drugs are different strengths or formulations. Officials told us that there is no shortage, from DEA's perspective, as long as there is quota available to

⁷⁸Collaboration can be broadly defined as any joint activity that is intended to produce more public value than could be produced when the organizations act alone, including coordination.

⁷⁹See [GAO-06-15](#).

⁸⁰Pub. L. No. 112-144, § 1004, 126 Stat. at 1104-05 (codified at 21 U.S.C. § 356e) (directing the Secretary of Health and Human Services to “maintain an up-to-date list of drugs that are determined by the Secretary to be in shortages in the United States” among other things).

manufacture a given controlled substance, regardless of which manufacturers are producing the product and which strengths or formulations are available. For instance, DEA would not consider there to be a shortage of 1 milliliter vials of hydromorphone in the 10 milligram/milliliter concentration if the 5 milliliter vials were still available. Separately, FDA evaluates potential substitutes on a case by case basis to determine whether drugs are clinically interchangeable in order to assess if there is enough supply of a drug to meet demand. To determine clinical interchangeability, FDA states that it relies upon clinical expertise from within the agency, as well as consultation with outside medical professional associations. For example, for ADHD drugs, both the immediate release and extended release formulations are needed and are not substitutes for each other. According to FDA, some patients are well maintained on the extended release formulation alone, some patients require the immediate release formulation at certain points in the day to treat their specific symptoms, and some patients require both the extended release formulation as well as the immediate release formulation at specific times of the day to control their symptoms. FDA may or may not consider drugs of different strengths or formulations to be substitutes for one another and FDA's determination about whether drugs are clinically interchangeable has not always aligned with DEA's perspective, leading DEA to assert that some of the shortages listed on FDA's website are not actual shortages. By not reaching an agreement about what constitutes a drug shortage, the agencies are lacking a key practice of effective coordination and it is unclear if they will be able to work together to respond to shortages of drugs containing controlled substances caused by quotas.

The agencies' collaboration is further impaired by a lack of trust on the part of DEA regarding the shortages listed on FDA's drug shortage website. DEA officials told us that they do not believe FDA appropriately validates or investigates the shortages it lists on its website, which they believe encourages abuse by manufacturers and distributors. Specifically, DEA officials said that they are concerned that manufacturers may falsely report shortages to FDA when they do not receive the amount of quota they requested, rather than because there are actual supply disruptions. As DEA does not consider FDA to have independently confirmed the existence of a shortage, DEA officials said that it considers FDA's website to be an incentive for manufacturers to file self-serving and misleading reports. As a result, despite the fact that DEA officials told us they monitor FDA's website, they still consider it to be neither useful nor accurate for DEA's purposes. When we spoke to FDA about its drug shortage website, officials told us that the agency takes multiple steps to verify the existence

of a shortage before placing it on its website, including confirming the supply disruption with the manufacturer of the product, checking with manufacturers of related products to confirm that they cannot cover the decrease in supply, and analyzing market sales data to compare current supply with historical demand.⁸¹

Another barrier to effective collaboration is the lack of compatible policies, procedures, and other means to operate across agency boundaries, including mutually agreed upon time frames for DEA to respond if FDA notifies DEA of a shortage caused by quota. Although FDA established policies and procedures in September 2014 for requesting a quota adjustment from DEA if it determines that it is necessary to address a shortage, DEA officials said that the agency has not and does not plan to establish formal policies or procedures to coordinate the agency's response with FDA.⁸² Such actions are not consistent with key practices for effective collaboration. It is important to note that while FDASIA directs DEA to respond within 30 days to manufacturers that request additional quota pertaining to a drug in shortage that is on FDA's drug shortage list, the law does not specify how quickly DEA must respond to a request from FDA to address a shortage of a life-sustaining drug and the agencies do not have an agreement in place regarding this matter. A time frame for DEA to respond to an FDA request is particularly important, given that FDA has determined that there is a shortage of a life-sustaining drug that an increase in quota is necessary to address, and DEA may not necessarily agree with FDA's determination of a shortage. Federal standards for internal control also state that communicating information within a specified time frame that enables entities to carry out their responsibilities is an important control activity.⁸³ DEA officials told us that the notifications it received from FDA prior to FDASIA were not useful. These notifications included copies of manufacturers' quota applications and FDA's assessment that the application was, or could be, related to a shortage. DEA maintained that, because FDA was not providing it with any new information, FDA's notifications were not helpful. Further, DEA

⁸¹For more information on the steps that FDA takes to verify the existence of a drug shortage see [GAO-14-194](#).

⁸²See FDA, *Manual of Policies and Procedures, Drug Shortage Management*, MAPP 4190.1 Rev. 2 (Sept. 3, 2014).

⁸³See [GAO/AIMD-00-21.3.1](#), 18.

officials said that the applications may or may not be related to a shortage from DEA's perspective.

Finally, both agencies stated that they are subject to restrictions on exchanging the proprietary information they receive from drug manufacturers. Both agencies agree that sharing such information with one another would be helpful in preventing and mitigating shortages of drugs containing controlled substances. For example, DEA officials said that it would be helpful to be informed in advance of FDA's decisions about upcoming drug approvals that may help alleviate a shortage. According to DEA, this could provide it with early notification about the need to quickly verify information provided by manufacturers in quota applications for drugs that appear to be nearing FDA approval. DEA officials added that such information sharing would make it easier for the two agencies to communicate about drug shortages and quotas in a meaningful way.

Although DEA and FDA have long had memorandums of understanding (MOU) in place, these documents do not address the topic of drug shortages. The agencies have been working for more than 2 years on developing a new MOU, which would replace the original documents that were executed in the 1970s. As of January 20, 2015, the new MOU had not been finalized and the two agencies report that they are continuing to work towards outlining mutually agreeable terms. Officials from both agencies explained that they expect the new MOU would establish the terms for sharing and safeguarding the proprietary information that they are currently prohibited from exchanging and that may ultimately allow the agencies to work together more effectively to address shortages. However, DEA officials said that they do not expect the new MOU to specify what types of information may be shared, including information related to a shortage of a drug containing controlled substances or the time frames for sharing such information. FDA officials indicated that once the new MOU is in place the two agencies will still need to take additional steps before they can begin to share information, such as developing a work plan for sharing information related to shortages of drugs containing controlled substances. As the agencies will need to take additional steps before they can begin exchanging information related to shortages after the MOU is in place, it is uncertain whether FDA and DEA will be able to expeditiously address shortages of drugs containing controlled substances, should one occur in the near future.

Conclusions

Prescription drugs containing controlled substances are routinely used in inpatient, outpatient, and emergency settings. DEA is responsible for preventing, detecting, and investigating the diversion of these substances, while nonetheless ensuring an adequate and uninterrupted supply for legitimate needs. Because DEA maintains a closed system of distribution that limits the availability of certain substance classes by establishing aggregate production, bulk manufacturing, and procurement quotas, the agency's management of the quota process is of critical importance to public health.

Our work shows that DEA is not well prepared to expeditiously respond to future shortages. DEA has not met its required time frames for establishing quotas for more than a decade. DEA also lacks sufficient internal controls to ensure the reliability of the data it uses to establish quotas, which we found led to errors in its data system. Moreover, DEA does not monitor the data it collects and has no established performance measures related to either setting quotas in a timely manner or ensuring an adequate and uninterrupted supply of controlled substances for legitimate medical use. Its lack of written policies and procedures for a complex process poses a risk to the continuity of its future operations.

Because FDA also plays a vital role in preventing, mitigating, and resolving drug shortages, its collaboration with DEA is key to responding to shortages. FDA adopted the definition of a drug shortage that is specified in FDASIA and was assigned authority to maintain the list of drugs in shortage. Moreover, FDASIA directs the two agencies to work together to coordinate certain activities related to shortages. However, DEA and FDA are not able to effectively collaborate due to fundamental disagreement over whether any given shortage exists. DEA has made it clear it does not trust FDA's information, as it does not consider many of the shortages that FDA verifies to be legitimate. In addition, DEA has not developed any formal policies or procedures to coordinate its response to a shortage with FDA. The two agencies have been operating under an MOU that has been unchanged for about 40 years and that does not address the topic of drug shortages. Although it is under revision, this process began over 2 years ago and remains incomplete. Despite FDASIA's provisions directing the two agencies to coordinate and report on their responses to drug shortages, it is not clear that the new MOU will facilitate this. Given that the agencies have indicated that they will still need to take additional steps before they can begin exchanging information after the MOU is in place, they may not be able to provide a quick response should a shortage occur in the near future.

While we cannot establish a causal relationship between shortages of drugs containing controlled substances and DEA's management of the quota setting process, the shortcomings we have identified prevent DEA from having reasonable assurance that it is prepared to help ensure an adequate and uninterrupted supply of these drugs for legitimate medical need, and to avert or address future shortages. This approach to the management of an important process is untenable and poses a risk to public health.

Recommendations for Executive Action

To ensure that DEA is best positioned to administer the quota process to ensure an adequate and uninterrupted supply of controlled substances for legitimate medical use and respond to shortages of drugs containing controlled substances, we recommend that the Administrator of DEA take the following five actions:

- establish controls, including periodic data checks, to ensure that the YERS/QMS data accurately reflect both manufacturers' quota submissions and DEA's decisions;
- establish performance measures for DEA related to quotas and ensuring an adequate and uninterrupted supply of controlled substances for legitimate medical use;
- monitor and analyze YERS/QMS data to assess DEA's administration of the quota process;
- establish internal policies for processing quota applications and setting aggregate, annual, and supplemental quotas to ensure that staff conduct these activities consistently and in accordance with the CSA and agency's regulations; and
- expeditiously establish formal policies and procedures to facilitate coordination with FDA as directed by FDASIA, including a specific time frame in which DEA will be expected to respond to FDA requests to expedite shortage-related quota applications.

To strengthen DEA's and FDA's ability to respond to shortages of drugs containing controlled substances, we recommend that the Administrator of DEA and the Commissioner of FDA take the following two actions:

- promptly update the MOU between the two agencies, and
- either in the MOU or in a separate agreement, specifically outline what information the agencies will share, and time frames for sharing such information, in response to a potential or existing drug shortage.

Agency Comments and Our Evaluation

We provided a draft of this report for comment to HHS and DOJ. In addition, we provided excerpts of this report to UUDIS. We received written comments from HHS and DEA, which are reproduced in full in appendix IV and V, respectively. Both agencies also provided technical comments, which we incorporated as appropriate. UUDIS did not have any comments.

HHS agreed with the two recommendations applicable to FDA. Specifically, it agreed with our recommendation that it promptly update its MOU with DEA. It also agreed with our recommendation that it and DEA should specifically outline what information they will share and the time frames for doing so, in response to a potential or existing drug shortage. HHS also stated that FDA is actively working to finalize the new MOU with DEA.

DEA did not explicitly agree or disagree with the seven recommendations we made to it, but commented on each. In some instances, its comments indicate that it is either supportive of strengthening its management of the quota process and improving coordination with FDA, or that it has already taken steps consistent with our recommendations. In one instance, it did not respond directly to our recommendation. DEA also raised multiple objections to our work and described what it characterized as flaws and weaknesses in our draft report. In particular, DEA stated concerns with (1) our understanding of quotas, (2) definition of a shortage, (3) the title of our draft report, (4) our methods of conducting investigation and data analysis, and (5) our conclusions.

Understanding of quotas. DEA stated that we fail to understand that it does not have the authority to issue quotas for individual dosage forms and that it cannot require a manufacturer to manufacture or distribute its products, whether API or final dosage form. This report reflects these facts, specifically stating that “DEA does not have the authority to issue quotas for specific products or to require manufacturers to use their quota for specific products.” DEA concluded that because the agency does not have this authority, its quota decisions have no effect on the availability of individual dosage forms containing substances that are subject to quotas. We disagree with this conclusion because manufacturers must receive authorization from DEA to obtain controlled substances subject to quotas, and so the amounts of quota authorized by DEA and the timing of its decisions directly affect when manufacturers are able to obtain the substances necessary to manufacture their products. We understand that manufacturers are ultimately responsible for what they manufacture with

the quota authorized by DEA, but their decisions are made within the confines of the quota granted by DEA.

Definition of a shortage. DEA stated that our draft report is misleading because we fail to account for the fact that the definition of a “shortage” means different things to different entities. DEA suggested that our approach is flawed because we focus on individual drug products rather than the basic class of controlled substances. We do so because this is the level that affects patients and providers. Thus, we used data from UUDIS and FDA, both of which track shortages of individual drug products. UUDIS is regarded as the most comprehensive and reliable source of drug shortage information between January 2001 through June 2013 and FDA has been mandated by statute to identify and monitor drug shortages. Drugs within the same substance class are not necessarily clinically interchangeable, according to FDA and UUDIS. For example, as we describe in this report, there can be significant implications for patients who have to switch from an extended-release formulation to an immediate-release formulation of the same drug and patients who have trouble swallowing may not be able to use a tablet formulation if an injection is in short supply.

Additionally, DEA criticized our use of FDA’s revised definition of a drug shortage, which FDA adopted in September 2014. DEA stated that this definition, which FDA adopted to be consistent with FDAISA, is “materially different” from the definition FDA used from 2006 through 2012. DEA implied that, by doing so, our analysis was flawed in that we inappropriately applied the new definition to our analysis of YERS/QMS records from 2011 and 2012—a period predating FDA’s revised definition. We disagree. Our analysis of certain YERS/QMS records was premised on particular shortages of drugs containing controlled substances that occurred between January 2010 and June 2013. We collected data from FDA beginning in October 2012 to specifically identify the manufacturer-reported causes of shortages of drugs containing controlled substances. We completed our collection of FDA’s data in August 2013. We could not have applied FDA’s revised definition of a drug shortage to our efforts as, at that time, the revised definition was not yet adopted by FDA. We requested the YERS/QMS source documents, including the entire population of records in 2011 and 2012 that were associated with drug shortages manufacturers reported to FDA that were caused by quotas, in June 2014. Therefore, FDA’s revised definition had no bearing on our YERS/QMS analysis. However, we include and discuss FDA’s revised definition in this report as it is relevant to FDA’s and DEA’s implementation of FDASIA provisions that require coordination between

both agencies in response to certain drug shortages. It is also important to note that, although DEA asserts that FDA's revised definition is "materially different" than its prior one, as we note in this report, FDA does not consider the revised definition to be substantively different nor does it alter how FDA works to resolve drug shortages.

With respect to DEA's and FDA's different views on when a shortage exists, our report explicitly recognized that DEA and FDA are not able to effectively collaborate due to this fundamental disagreement. In fact, this was the basis for our recommendation that DEA and FDA take steps to improve the coordination required of them under FDASIA.

Title of our draft report. DEA stated that the title of our draft report was inconsistent with our findings: (1) that a causal relationship could not be established between shortages of drugs containing controlled substances and DEA's lack of timeliness in establishing annual and supplemental quotas and (2) that we could not prove that DEA's collaboration with FDA would hinder their collective abilities to effectively coordinate regarding future shortages. We disagree with DEA's conclusion that the quota process and its collaboration with FDA play no role in, and cannot cause or exacerbate, drug shortages. As this report shows, DEA does not use effective approaches for managing the quota process or collaborating with FDA. We continue to believe that DEA should improve its administration of the quota process and enhance coordination with FDA to be in a position to fulfill its statutory responsibilities. Nevertheless, we modified the title of this report to emphasize the need for process and collaboration improvements, rather than the link between drug shortages and the process and collaboration shortcomings.

Method of conducting investigation and data analysis. DEA stated that our methodology was flawed because we did not attempt to independently determine whether there were shortages of drugs subject to quotas and whether quotas actually caused such shortages. In its comments, DEA stated that two of its data systems—ARCOS and YERS/QMS—would have provided us with such information. This stance contradicts information that DEA consistently provided throughout the course of our work, and we disagree with DEA's position for several reasons.

- First, we sought to obtain ARCOS and YERS/QMS data from DEA early in our review and were met with strong opposition from agency officials. We requested ARCOS data in order to track the drugs that

manufacturers reported to be in shortage to examine their movement through the supply chain before, during, and after the reported shortage and YERS/QMS data to analyze DEA's timeliness and responsiveness in authorizing quota. DEA officials said that ARCOS is used to monitor the diversion of drugs and it is not used nor intended to be used to identify shortages of specific drugs. DEA officials also told us that there is too much complexity in the supply chain to perform a meaningful analysis and that it would be inappropriate to use ARCOS data for our purpose. DEA officials also insisted that supplying us with ARCOS data would be burdensome and an inefficient use of their agency's resources. Similarly, DEA officials objected to providing us with the YERS/QMS data we requested. As DEA stated in its comments, negotiations to obtain these data were "protracted and contentious." Our audit was ultimately delayed for over a year as we attempted to obtain these ARCOS and YERS/QMS data. However, following the intervention of senior DOJ management officials, DEA eventually provided the requested information from both ARCOS and YERS/QMS.

- Second, although DEA indicated in its comments that ARCOS and YERS/QMS data could have provided us with a "full view" of the distribution of schedule II controlled substances throughout the supply chain, this is inconsistent with information the agency provided throughout the course of our work and what we ultimately found through our analyses. DEA officials repeatedly informed us that, apart from their concerns with providing us with the ARCOS data, they objected to our planned analysis because of significant and inherent inaccuracies in the data. Agency officials explained that, because the ARCOS data are self-reported by registrants, the data contain many errors, particularly in the quantity field that records the number of packages, weight, or volume being reported in each transaction. DEA officials told us that they consider these data to be so unreliable they only use data from ARCOS as a preliminary tool when beginning diversion investigations, and that they must ultimately verify the data against source documents available at the registrants' business locations. DEA advised us that ARCOS data were unreliable; however, to maintain our independence, it was necessary for us to obtain a sample of data to complete our own assessment.

Once we obtained the requested data from both ARCOS and YERS/QMS, we conducted a preliminary analysis on each data set. We identified significant data reliability issues with both sets of data and determined that both ARCOS and YERS/QMS were unreliable for our purposes. Specifically, regarding ARCOS, our analysis of the data sample identified drastically different numbers of transactions and

amounts reported as transferred between manufacturers and distributors for any given quarter between 2010 through 2012. Both manufacturers and distributors are required to report the number of transactions of these substances and the amounts transferred to ARCOS, so we would therefore expect that the number of transactions and amounts reported as transferred between both groups to be similar. DEA officials could not provide explanations for these inconsistencies. In addition, it was not possible for us to use source documents to verify all of the transactions in our sample because it was beyond the two year retention requirement for registrants' original documentation for many of the transactions. Because our tests on the sample we obtained showed the ARCOS data to be unreliable for our purposes, there was no point in further analyzing ARCOS data or in requesting additional data.

Our assessment of YERS/QMS also determined that these data were not reliable for our purposes. However, we were able to analyze a sample of YERS/QMS data by taking certain methodological steps. Specifically, to correct for the errors that we found in the data, we analyzed the information contained in the source documents for our sample of YERS/QMS records for certain fields. Overall this sample represented about 15 percent of the total YERS/QMS records that we obtained from DEA in 2011 and 2012.⁸⁴ We found a significant number of errors in the data from 2011 (44 percent overall) and less in the data from 2012 (10 percent overall). Although we had correct information from the source documents, we determined that it was not appropriate for us to use all of the fields contained in those documents because we continued to identify inconsistencies, including in the source documents themselves. For instance, within the source documents associated with a particular supplemental application—a manufacturer's supplemental quota application and DEA's decision letter—the manufacturer may have requested the additional amount of quota it was seeking (e.g., an additional 500 grams in addition to 500 grams it previously received), but DEA's corresponding decision letter authorized the total amount of quota for that year (e.g., 1,000 grams). Therefore, it would appear that DEA authorized 200 percent of the quota requested in this case, according to the source documents, when in fact it authorized 100 percent of the request. Due to these

⁸⁴According to DEA officials, YERS/QMS data prior to 2011 were not available and our data request was made before 2013 was complete.

inconsistencies, we did not pursue analyzing the amount of quota that DEA authorized for manufacturers in 2011 and 2012. DEA states in its comments that we should have analyzed the amounts of quota authorized by DEA for the substance classes that had drugs in shortage in 2011 and 2012 to verify the manufacturers' claims that quotas caused or exacerbated shortages. However, the data reliability concerns we identified within the quota amount fields, particularly for 2011 data when 6 of the 7 quota related shortages began, prevented the feasibility of a meaningful analysis.

In addition to criticizing our methodology for not fully utilizing data from YERS/QMS and ARCOS to independently establish causation between a specific shortage and the quotas DEA established for a basic class of schedule II controlled substance, DEA stated that our draft report was misleading because of our extensive description of the nature and magnitude of drug shortages of all controlled substances and their consequences. We do so because the scope of this report is not limited to drugs containing controlled substances that are subject to quota, but includes other prescription drugs containing controlled substances. It is important to note that we identify specific examples of shortages of schedule II drugs that are subject to quota—such as morphine, fentanyl (anesthesia), amphetamine and methylphenidate (ADHD drugs)—and the impact of these shortages on patients and providers in this report. As we note in this report, quota was not reported to be the primary cause of all shortages of drugs that contain schedule II substances. Indeed, not all drugs containing controlled substances are subject to quota. Other primary causes included manufacturing delays, capacity issues, and product quality issues, which are the same factors that cause shortages of drugs generally. However, because the availability of quota could be a factor in shortages of those drugs that do contain controlled substances subject to quota, we considered it both necessary and relevant to include such information. We therefore provide FDA data on the manufacturer-reported causes of shortages of their products containing schedule II substances, including quota.

Lastly, we believe that DEA may have misconstrued the intent of our study. DEA implies that our purpose was to evaluate whether it authorized adequate amounts of quota and whether manufacturers provided adequate justification for their quota requests. However, our purpose was to examine the trends and characteristics of drug shortages of controlled substance and their affect on patients and providers, as well as assess DEA's administration of the quota process, including its internal controls and compliance with required time frames. The purpose of our

study was not to determine whether DEA's decisions were correct or manufacturers' justifications were sufficient. In using ARCOS and YERS/QMS data, we sought to obtain information about where certain controlled substances were in the supply chain before, during, and after a shortage and DEA's timeliness and responsiveness in responding to manufacturers' quota applications. Data reliability concerns with both data sets prevented us from fully accomplishing such analyses.

Our conclusions. DEA stated that our conclusions unfairly link the quota process to diminished patient care by describing the trends of shortages of drugs containing controlled substances and then evaluating DEA's administration of the quota process that only applies to a subset of those substances. These are two separate issues. This report does not say, nor do we believe, that quotas are the sole cause of shortages of drugs containing schedule II substances. However, we disagree with DEA's contention that the actions it takes in setting quotas at the class level would have no bearing on the drug products that are made with those substances. The shortcomings that we identified in DEA's administration of the quota process prevent it from having reasonable assurance that it is providing for an adequate and uninterrupted supply of these drugs for legitimate medical need, and calls into question DEA's ability to avert or address future shortages of medically necessary products. We agree that there are many factors that affect and ultimately cause drug shortages and include these in this report. However, simply because not all drugs that have been in shortage are subject to quotas does not mean that quotas cannot cause, contribute to, or exacerbate shortages of drugs containing schedule II substances.

DEA also questioned our conclusion that by not acting promptly to respond to supplemental quota applications, it may hinder manufacturers' ability to produce schedule II drugs that may help prevent or resolve a shortage. DEA said this is not possible because manufacturers' business decisions are involved. We recognize that manufacturers must apply for quota, and then use it to manufacture and ultimately distribute the appropriate drugs for there to be any impact on drug shortages. However, DEA's actions also play a part when quota is involved. DEA's lack of timeliness in responding to manufacturers' supplemental quota applications—taking nearly 60 days on average—for both shortage and non-shortage related applications is problematic and not in the interest of public health. We continue to believe DEA should implement our recommendations to ensure that it is positioned to comply with the statutorily mandated time frame of responding to applicable requests within 30 days.

DEA's response to our recommendations. Regarding our first recommendation that DEA establish controls to ensure that the YERS/QMS data accurately reflect both manufacturers' quota submissions and DEA's decisions, DEA described existing flags and reviews in place to ensure the information that is entered by manufacturers and DEA staff is accurate. While we understand that DEA takes some steps to help ensure the accuracy of YERS/QMS data, it does not perform sufficient checks to ensure the accuracy of the information. For example, DEA does not compare a sample of YERS/QMS data to the source documents (manufacturer's application and DEA decision letter) to identify if its existing checks are adequate. Although the accuracy of the data improved from 2011 to 2012, we nonetheless found a 10 percent error rate in the 2012 data. In particular, some of the fields with the highest rates of error in the 2012 data were in the fields for the amount of quota requested or authorized, which have implications for the availability of controlled substances subject to quota. We continue to believe that taking additional steps to reduce this error rate, as we recommended, is important.

Regarding our second recommendation to establish performance measures related to quotas, DEA said it recognizes the value in establishing performance measures for personnel who review quota applications. While we agree that it can be useful to develop performance measures for personnel, our recommendation is intended to be more expansive than that and should include performance measures at the program or agency level. For example, as we note in this report, DEA could set goals and then measure the number of manufacturers who submit incomplete or revised quota applications, both factors that DEA cited as affecting its ability to meet its required time frames. DEA could also establish goals and track the percentage of annual applications that DEA responds to in accordance with its required time frames. It is important that DEA set such measures to assess its performance in achieving its mission of ensuring an adequate and uninterrupted supply of controlled substances as it does for its diversion-related mission.

For our third recommendation about monitoring and analyzing YERS/QMS data, DEA said it agrees that such actions are important to ensuring proper administration of the quota process. DEA also provided examples of how the agency uses YERS/QMS data in setting APQs and bulk manufacturing and procurement quotas. However, the agency did not commit to using the data to monitor its administration of the quota process or its performance. Such information could be of vital importance to determine the feasibility of potential performance measures, as we

recommended, or to evaluate DEA's efforts in meeting its performance measures once developed, such as the extent to which DEA is meeting its required time frames for responding to annual quota applications.

In response to our fourth recommendation that DEA establish internal policies for processing quota applications, DEA stated that it has already established such policies and procedures. However, the agency did not provide documentation of such policies and procedures despite repeated requests. To the contrary, DEA officials told us that the agency relies exclusively on its regulations and the CSA in establishing APQs and manufacturers' quotas. As we state in this report, this is inconsistent with federal standards for internal control, and we believe that policies are still needed because of the complexity of the work involved in setting quotas.

In response to our fifth recommendation that DEA expeditiously establish formal policies and procedures to facilitate coordination with FDA as directed by FDASIA, DEA stated that it will follow the requirements of FDASIA to respond to FDA's requests within 30 days. However, FDASIA does not specify a time frame in which DEA must respond to FDA's requests to increase quota; this 30-day time frame is only applicable to requests that DEA receives from manufacturers. Furthermore, DEA has not historically met its required time frames for establishing quotas from either the CSA or its regulations. Therefore, we believe that policies and procedures are needed to establish such a time frame and specify how DEA will respond to such a request from FDA. We understand that DEA has received no such request from FDA since the enactment of FDASIA; however, we believe that it is imprudent to wait for a shortage that has serious implications for public health before determining how to proceed.

Regarding our sixth recommendation that DEA promptly update the MOU with FDA, DEA stated that it had begun negotiating the terms of the new information sharing agreement when this review began in 2012, which we note in this report. DEA said that the final version of this MOU has been routed for signature within the agency as of December 2014.

Lastly, in response to our seventh recommendation that, either in the MOU or in a separate agreement, DEA and FDA specifically outline what information the agencies will share and the time frames for sharing such information in response to a potential or existing drug shortage, DEA noted that it has already engaged in discussions with FDA to determine the specific procedures for sharing drug shortage related information pursuant to FDASIA. We believe that reaching a specific agreement on information sharing will be beneficial to both agencies.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies of this report to the Secretary of the Department of Health and Human Services and the Attorney General, and other interested parties. In addition, the report will be available at no charge on GAO's website at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or at crossem@gao.gov. Contact points for our Office of Congressional Relations and Office of Public Affairs can be found on the last page of this report. Other major contributors to this report are listed in appendix VI.

A handwritten signature in black ink that reads "Marcia Crosse". The signature is fluid and cursive, with a long horizontal line extending to the right from the end of the name.

Marcia Crosse
Director, Health Care

Appendix I: List of Provider and Patient Organizations Interviewed

Provider Organizations

1. American Academy of Child and Adolescent Psychiatry
2. American Academy of Pediatrics
3. American College of Emergency Physicians
4. American Hospital Association
5. American Psychiatric Association
6. American Society of Anesthesiologists
7. American Society of Health-System Pharmacists
8. Association of Critical Care Transport
9. Institute for Safe Medication Practices
10. International Association of Fire Chiefs
11. National Association of Boards of Pharmacy
12. National Association of Emergency Medical Technicians
13. National Association of State EMS Officials
14. National Community Pharmacists Association

Patient Organizations

1. Children and Adults with Attention Deficit/Hyperactivity Disorder
2. National Alliance on Mental Illness

Appendix II: Classes of Schedule II Controlled Substances with Medical Use

The Drug Enforcement Administration (DEA) establishes quotas on the quantity of schedule II substance classes that may be produced in the United States in any given calendar year.¹ We consider classes of schedule II controlled substances with medical use to be those substances that are contained in Food and Drug Administration (FDA) approved products currently marketed for human use, and are not considered precursors, reference standards, or metabolites, as reported by DEA.² Those substance classes include the following:

Alfentanil	Hydromorphone	Opium
Amobarbital	Levorphanol	Oxycodone
Amphetamine	Lisdexamfetamine	Oxymorphone
Cocaine	Meperidine	Pentobarbital
Codeine	Methadone	Remifentanil
Dihydrocodeine	Methamphetamine	Secobarbital
Diphenoxylate	Methylphenidate	Sufentanil
Fentanyl	Morphine	Tapentadol
Hydrocodone	Nabilone	

¹DEA also establishes quotas for schedule I substances, but we did not include them in our report because such substance classes have no currently accepted medical use in treatment in the United States.

²A precursor is a chemical that is transformed into another compound as in the course of a chemical reaction. For example, the controlled substance noroxymorphone is a precursor used to manufacture opiates. A metabolite is a substance produced during metabolism or a result of metabolism. For example, the substance ecgonine is a metabolite of cocaine as it is generated in the extraction of cocaine from coca leaf.

Appendix III: Scope and Methodology – Analysis of the Year-End Reporting and Quota Management System Data

As part of our work examining the Drug Enforcement Administration’s (DEA) quota process, we analyzed data from DEA’s Year-End Reporting and Quota Management System (YERS/QMS) for certain controlled substances with medical use to assess the reliability of the system and DEA’s timeliness in responding to manufacturers’ quota applications. This appendix provides further detail on our methods for determining the reliability of the data and analyzing the data.

To determine the reliability of data from DEA’s YERS/QMS, DEA provided data from the system for 2011 and 2012, the most recent years for which data were available when we began our analysis. We discussed these data with the officials responsible for maintaining YERS/QMS and examined the data for obvious errors and values outside of expected ranges. We removed applications that were marked as “withdrawn,” as DEA does not authorize quota for these applications.¹ We also removed applications that appeared to be duplicates, which we identified by searching for applications that had the same registrant, drug, date submitted, and quota type (e.g., bulk manufacturing or procurement). We searched for applications that had the word “duplicate” in the notes field of YERS/QMS as well, which DEA uses to record additional information about quota applications. Additionally, we removed applications that were not for schedule II substance classes with medical use.²

We then selected a sample of 442 records, from the total of 2,982 records, from YERS/QMS to verify against source documents, each of which includes a manufacturer’s quota application for a particular substance and the corresponding DEA decision letter informing the manufacturer of its quota authorization (see table 5). This sample included the entire population of records in 2011 and 2012 that are associated with drug shortages manufacturers reported to the Food and Drug Administration (FDA) were caused by quotas, of which there were 146. We consider YERS/QMS records to be associated with these shortages if the record contains a quota application that was (a) submitted by a manufacturer who reported to FDA that quota caused a shortage of its product; (b) for a substance that was used in the

¹DEA told us that manufacturers often withdraw an application if it has an error or if a manufacturer loses a contract and no longer needs quota for a particular substance.

²See appendix II for the list of schedule II substances that we consider to have medical use.

products reportedly in shortage because of quota; and (c) was submitted during the time of the reported shortage caused by quota. For instance, if a manufacturer reported a shortage of a drug containing a controlled substance to FDA beginning in 2011 and ending in 2012, and said that the shortage was caused by quota issues, we considered all applications from that manufacturer for that controlled substance in 2011 and 2012 to be related to a shortage reportedly caused by a quota issue. We also selected a random sample of 296 records stratified by year—182 and 114 records from 2011 and 2012, respectively. We included more records from 2011 because we believed those records would be harder for DEA to locate, as DEA told us that there were a larger percentage of hard-copy applications, as opposed to electronic applications, in 2011 than 2012. Because we followed a probability procedure based on random selections, our sample is only one of a large number of samples that we might have drawn. Since each sample could have provided different estimates, we express our confidence in the precision of our particular sample’s results as a relative margin of error based on a 95 percent confidence interval (e.g., plus or minus 10 percentage points). This is the interval that would be expected to contain the actual population value for 95 percent of the samples we could have drawn.

Table 5: Records Sampled from the Drug Enforcement Administration’s Year-End Reporting and Quota Management System (YERS/QMS) for Schedule II Substances with Medical Use

	Number of records in population	Number of records in sample
Records associated with shortages reportedly due to quota (2011 and 2012)	146	146
Records not associated with shortages reportedly due to quota (2011)	1,419	182
Records not associated with shortages reportedly due to quota (2012)	1,417	114
Total	2,982	442

Source: GAO analysis of YERS/QMS data. | GAO-15-202

From our sample of 442 YERS/QMS records for which we requested source documents from DEA, we analyzed source documents for 440 records. DEA officials said that they could not locate documents for one record and another record was found to be ineligible based on our review. Noncertainty sample sizes were inflated to account for an expected location rate of 50 percent for 2011 and 80 for 2012, to assure enough located files would be available for analysis. Because DEA told us that some paper applications had been put into storage due to office renovations and were difficult to retrieve, we assumed we would not be able to locate the full sample of records. DEA officials told us that there were more paper records—as opposed to electronic records—submitted

in 2011 than 2012. Based on that information, we assumed a lower location rate in 2011 than 2012. In order to estimate population quantities, we analyzed our sample data using survey analysis software that accounts for our stratified random selection design and uses analysis weights in order to make the results of our sample representative of all YERS/QMS applications for schedule II substances with medical use in 2011 and 2012.

In order to confirm that we were comparing the source documents to the correct record in YERS/QMS, we matched the documents based on the manufacturer and substance, and at least one of the following fields: date application was submitted; total amount requested; date decision letter was mailed; and total amount authorized.³ Using this methodology, we were able to match 440 records in our sample. To verify the accuracy of the YERS/QMS data for these 440 records, we compared the data in YERS/QMS against the information in DEA's source documents (quota applications and decision letters). We used the following fields in the quota application to validate or correct the data in YERS/QMS: quota year, company name, substance name, quota type (e.g., bulk manufacturing or procurement), the date submitted, and total amount requested. We used the following fields in the decision letters provided by DEA to validate or correct the data in YERS/QMS: quota year, company name, substance name, quota type (e.g., bulk manufacturing or procurement), date mailed, and total amount authorized. We calculated the number of fields with errors (e.g., number of errors in the date submitted field) and the number of records with errors (i.e., a record with an error in any field). We also weighted the results of our error calculations in order to make the results representative of all YERS/QMS records in 2011 and 2012. Based on our review of these source documents, we determined that the YERS/QMS data we obtained from DEA were unreliable for our purposes.

Because of the reliability concerns with the YERS/QMS data, we used the information contained in the 440 YERS/QMS source documents for our analysis of DEA's timeliness in responding to manufacturers' quota applications and when manufacturers submitted annual quota applications. In order to separate annual applications and supplemental

³DEA matched source documents to the corresponding YERS/QMS records for 8 of the 440 records for which they provided source documents.

applications, which have different requirements for timeliness, we considered annual applications to be applications submitted in the year prior to when the quota would be used (e.g., an application submitted in May 2010 for 2011 quota). Applications submitted in the same year as when the quota would be used were considered supplemental. For annual applications, we analyzed DEA's compliance with the required deadlines in the Controlled Substances Act and DEA's regulations, including how often DEA met the deadlines for our sample of records and how many days passed when it did not meet the deadlines.⁴ We also analyzed when manufacturers submitted their annual quota applications. For supplemental applications, we analyzed the amount of time that it took DEA to respond to supplemental applications in our sample. We used a two-tailed t-test to determine whether there was a statistical difference in the amount of time DEA took to respond to supplemental applications submitted by manufacturers that reported shortages due to quota compared to all other supplemental applications. For our analysis of these 440 YERS/QMS source documents, we express our confidence in the precision of our particular sample's results the same way in which we did for our analysis of the errors in the YERS/QMS data, as we described above.

⁴See 21 U.S.C. § 826(c); 21 C.F.R. §§ 1303.12 and 1303.21.

Appendix IV: 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

DEC 29 2014

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, "Controlled Substances: Better Management of the Quota Process and Enhanced Coordination between DEA and FDA Needed to Address Drug Shortages" (GAO-15-202).

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

Sincerely,

A handwritten signature in cursive script that reads "Jim R. Esquea".

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: CONTROLLED SUBSTANCES: BETTER MANAGEMENT OF THE QUOTA PROCESS AND ENHANCED COORDINATION BETWEEN DEA AND FDA NEEDED TO ADDRESS DRUG SHORTAGES (GAO-15-202)

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity to review and comment on this draft report.

GAO Recommendation

To strengthen the Drug Enforcement Administration's (DEA) and the U.S. Food and Drug Administration's (FDA) ability to respond to shortages of drugs containing controlled substances, we recommend that the Administrator of DEA and the Commissioner of FDA promptly update the memorandum of understanding (MOU) between the two agencies and either in the MOU or in a separate agreement, specifically outline what information the agencies will share, and timeframes for sharing such information, in response to a potential or existing drug shortage.

HHS Response

HHS concurs with this recommendation and is actively working to finalize the new MOU with the DEA.

Appendix V: Comments from the Drug Enforcement Administration



U. S. Department of Justice
Drug Enforcement Administration

www.dea.gov

DEC 29 2014

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

Dear Ms. Crosse:

The Drug Enforcement Administration (DEA) provides the following comments to the Government Accountability Office (GAO) report entitled "*Controlled Substances: Better Management of the Quota Process and Enhanced Coordination between DEA and FDA Needed to Address Drug Shortages*" (GAO-15-202).

It is important to note that the titled conclusion of the report is inconsistent with the GAO finding that it cannot establish either a "causal relationship between shortages of drugs containing controlled substances and DEA's management of the quota setting process" (Draft, p. 45) or that DEA coordination with the U.S. Food and Drug Administration (FDA) adversely affected the availability of drug products containing controlled substances.¹

Introduction

The DEA agrees that prescription drug abuse is a nationwide epidemic and more must be done to prevent, detect, and deter the diversion of pharmaceutical controlled substances that supply drug addiction and abuse. The DEA role in this effort is as the primary agency responsible for coordinating the drug law enforcement activities of the United States. The Diversion Control Program (DCP) is a strategic component of the DEA's law enforcement mission. The DEA Office of Diversion Control administers the DCP and implements and enforces Titles II and III of the Comprehensive Drug Abuse Prevention and Control Act of 1970, as amended. 21 U.S.C. 801-971. Titles II and III are referred to as the "Controlled Substances Act" and the "Controlled Substances Import and Export Act," respectively, but are collectively referred to as the "Controlled Substances Act" or the "CSA." The CSA and its implementing regulations are designed to prevent, detect, and deter the diversion of controlled substances and listed chemicals into the illicit market while

¹ See Draft, p. 34 (stating GAO "cannot confirm whether DEA's lack of timeliness in establishing annual and supplemental quotas has caused or exacerbated shortages"); p. 40 (stating "DEA and FDA have not established a sufficiently collaborative relationship, which *could* hinder their abilities to effectively coordinate *future* shortages") (emphasis added).

Joseph T. Rannazzisi, Deputy Assistant Administrator

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establishing the total quantity of each basic class² of controlled substance in schedules I and II and for ephedrine, pseudoephedrine, and phenylpropanolamine to be manufactured each year to provide for the estimated medical, scientific, research, and industrial needs of the United States, for lawful export requirements, and for the establishment and maintenance of reserve stocks. This is a delicate balance.

One way that DEA provides for the estimated medical, scientific, research, and industrial needs of the United States is to establish an aggregate, nationwide quota for each basic class of schedule I and II controlled substance (referred to as the Aggregate Production Quota, or "APQ") and to authorize individual quotas (referred to as manufacturing quota and procurement quota). It is important to understand that DEA authorizes quota only at the manufacturer level for those entities that manufacture active pharmaceutical ingredients (API), those entities that manufacture substances into dosage forms, and those entities that repackage or re-label drug products that contain schedule I or II controlled substances. Once the aggregate quota is established and a particular manufacturer is

² "Basic class" means, as to controlled substances listed in Schedules I and II:

- (1) Each of the opiates, including its isomers, esters, ethers, salts, and salts of isomers, esters, and ethers whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation, listed in §1308.11(b) of this chapter;
- (2) Each of the opium derivatives, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation, listed in §1308.11(c) of this chapter;
- (3) Each of the hallucinogenic substances, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation, listed in §1308.11(d) of this chapter;
- (4) Each of the following substances, whether produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis:
 - (i) Opium, including raw opium, opium extracts, opium fluid extracts, powdered opium, granulated opium, deodorized opium and tincture of opium;
 - (ii) Apomorphine;
 - (iii) Codeine;
 - (iv) Etorphine hydrochloride;
 - (v) Ethylmorphine;
 - (vi) Hydrocodone;
 - (vii) Hydromorphone;
 - (viii) Metopon;
 - (ix) Morphine;
 - (x) Oxycodone;
 - (xi) Oxymorphone;
 - (xii) Thebaine;
 - (xiii) Mixed alkaloids of opium listed in §1308.12(b)(2) of this chapter;
 - (xiv) Cocaine; and
 - (xv) Ecgonine;
- (5) Each of the opiates, including its isomers, esters, ethers, salts, and salts of isomers, esters, and ethers whenever the existence of such isomers, esters, ethers, and salts is possible within the specific chemical designation, listed in §1308.12(c) of this chapter; and
- (6) Methamphetamine, its salts, isomers, and salts of its isomers;
- (7) Amphetamine, its salts, optical isomers, and salts of its optical isomers;
- (8) Phenmetrazine and its salts;
- (9) Methylphenidate;
- (10) Each of the substances having a depressant effect on the central nervous system, including its salts, isomers, and salts of isomers whenever the existence of such salts, isomers, and salts of isomers is possible within the specific chemical designation, listed in §1308.12(e) of this chapter. 21 C.F.R. § 1300.01(b).

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authorized to manufacture a specific amount of a basic class of controlled substance, DEA cannot require the manufacturer to manufacture API or a specific drug product, or distribute that substance down through the supply chain. Furthermore, a bulk manufacturer may extract or synthesize API in an authorized calendar year, and hold it in inventory until any subsequent calendar year. Of equal importance, the CSA prohibits DEA from establishing quotas in terms of individual pharmaceutical dosage forms prepared from or containing such a controlled substance. 21 U.S.C. § 826(a). These limitations are critical to understanding the effect that quota can have on the availability of a specific drug product at the retail level or at the emergency medical service (EMS) provider level. The failure to appreciate these limitations is the fatal flaw in the GAO report.

Another fundamental weakness in the GAO report is the failure to account for the fact that “shortage” means different things to different entities, and without accounting for this distinction, the GAO report is misleading with respect to the effect that the DEA quota process can have on patient care. To identify trends in shortages of drugs containing controlled substances, GAO analyzed University of Utah Drug Information Service (UUDIS) data. UUDIS broadly defines a “shortage” as a supply issue that affects how pharmacies prepare and dispense a product or that influences patient care when prescribers must choose an alternative therapy because of a supply issue. A UUDIS “critical shortage” occurs when alternative medications are unavailable, the shortages affect multiple manufacturers, or the shortages are widely reported. In addition, UUDIS information is based on national drug codes (NDCs) rather than the basic class of controlled substance contained within a specific drug product. NDCs are identifiers that are unique to a particular manufacturer, drug product, dosage form, dosage strength, and package size. Accordingly, a single basic class of controlled substance will be represented by many different NDCs. Statistics and analysis based on the NDC, rather than the basic class of controlled substance, could dramatically distort the actual number of shortages that could be attributed to quota.

From September 2006 through July 2012, the FDA defined a “drug shortage” as a “situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the user level.”³ (FDA CDER MAPP 6003.1, Sept. 26, 2006). FDA changed their definition in September 2014 to align with the definition in the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) to “a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug.” Although this new definition is materially different from the definition applicable during the period in review (2011 and 2012), the GAO report uses the 2014 definition in its analysis.

In contrast to the UUDIS and FDA, which view shortages in the context of patient-level availability, DEA views shortages in the context of manufacturer-level quota. Accordingly, a shortage within DEA’s jurisdiction is the lack of sufficient quota available for bulk or dosage form manufacturers to manufacture a basic class of a schedule I or II controlled substance. This perspective is the result of the CSA prohibition against establishing quotas in terms of individual

³ The GAO report discusses DEA’s concern with the reliability of information posted on FDA’s drug shortage website. During the period under review, DEA was concerned that FDA did not adhere to the applicable definition of “drug shortage” because FDA was listing drug products in shortage when clinically interchangeable drug products were available. Other inaccuracies included reporting that some distributors experienced a shortage due to quota or lack of API, yet distributors do not receive quota.

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pharmaceutical dosage forms prepared from or containing a controlled substance, together with the mandate to limit the supply of controlled substances available for diversion, and the inability to require a manufacturer to manufacture a specific API or drug product or require the distribution of controlled substance drug products downstream. Accordingly, if alternative forms of a drug product are available (e.g., brand, generic, or other clinically interchangeable drug products), or if manufacturers have quota authorization, the DEA cannot remedy any patient-level shortage (e.g., inadequate supply at the retail level or EMS provider level) by increasing the aggregate or authorizing more quota at the manufacturer level. GAO fails to emphasize and account for these fundamental distinctions in its review of the potential effect of the quota process on the availability of drug products containing schedule II controlled substances.

Some simplified examples can illustrate how the above distinctions can skew shortage conclusions. If there is an unmet patient need for hydromorphone 10 mg/mL, 1 mL vials, UUDIS and FDA would qualify it as a shortage. However, DEA would not consider there to be a shortage within its jurisdiction if the 10 mg/mL, 5 mL vials are available. Similarly, DEA would not consider there to be a shortage if the brand name version of a particular drug product is unavailable, if the generic version of the drug product is available. Also, there would be no shortage in DEA's jurisdiction if there is hydromorphone quota available in the APQ (i.e., the annual APQ has not been exhausted) and manufacturers are not requesting additional quota, or if manufacturers with authorized hydromorphone quota are not manufacturing their quota allotment or are not distributing the manufactured hydromorphone downstream.

Further comments regarding the GAO report are focused on the following three main areas and are discussed below: method of conducting investigation; method of data analysis; and GAO conclusions.

Method of conducting investigation:

Generally, the Congressional requesters sought to "better understand the impact of DEA quotas on patients with emergency medical and critical care conditions and traumatic injuries, and the extent to which DEA policies and regulations may impede the ability of physicians and health care providers to mitigate a shortage of a drug on any of the applicable schedules." Specifically, GAO was asked to particularly focus on shortages of drugs containing controlled substances used by EMS providers and to treat attention deficit hyperactivity disorder (ADHD). GAO did not evaluate the flow of specific controlled substances from the point of quota request and authorization to manufacture, or from the point of manufacture to distribution to the retail level, using available data from the Automation of Reports and Consolidated Orders System (ARCOS) and Year End Reporting and Quota Management System (YERS/QMS).

GAO was aware of which manufacturers self-reported shortages to FDA claiming the shortage was due to quota, and which specific drug products were reported in shortage due to quota, yet GAO did not investigate each manufacturer's quota allotment or usage, the manufacturer's manufacturing and distribution practices, whether the manufacturer provided adequate justification for quota, or if the manufacturer asked for quota before or after reporting the shortage. In fact, GAO did not attempt to determine whether "shortages" actually existed because of a lack of quota. GAO was not without the tools to determine the answer to this question. After a protracted and contentious

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negotiation regarding the data that DEA could release to GAO to conduct this investigation, DEA and GAO reached an agreement wherein DEA provided specified information from ARCOS and YERS/QMS. ARCOS and YERS/QMS data could have provided GAO with a full view of the distribution of schedule II controlled substances by manufacturers and distributors, from the point of bulk manufacture, to dosage form manufacture, and down to distribution to the retail level. Instead, GAO simply reported manufacturers' anecdotal complaints about the quota process' effect on shortages.

Amphetamine is a schedule II controlled substance and is used to treat ADHD, among other things, and it was reported to be in shortage during the review period. GAO requested ARCOS information pertaining to 17 specific NDCs, all of the amphetamine basic class. However, the 17 requested NDCs represented only a small fraction of the available market supply. The DEA estimated that there were 48 other amphetamine-containing drug products, 25 of which were manufactured and distributed during the period under review. GAO did not request ARCOS data on the other available amphetamine-containing products on the market, and GAO did not discuss in its report any findings relative to the 17 requested NDCs. The ARCOS information, combined with information from YERS/QMS, is crucial to determining whether sufficient API was manufactured, whether the API was distributed downstream by bulk manufacturers, whether dosage form manufacturers were manufacturing drug products in accordance with their quota applications, whether dosage form manufacturers were distributing drug products downstream and if so, where, and whether controlled substances were being held at the manufacturer level or destroyed rather than placed into the supply chain.

DEA is confident that a review of ARCOS and YERS/QMS data would have established that DEA's administration of the quota process did not cause or exacerbate any shortages of drug products used to treat ADHD in 2011. In 2011, DEA increased the APQ for amphetamine salts by 6,700 kg. A review of the ARCOS and YERS/QMS data for amphetamine salts showed that manufacturers subsequently requested, and DEA authorized, only a very small percentage of this increase. In addition, a significant number of amphetamine dosage units were destroyed throughout 2011, as well as a substantial amount of raw material, and millions of dosage units of ADHD drug treatment products still remained at the distributor and retail level at the end of 2011.

Close review of the ARCOS data would have also refuted manufacturers' assertions about the effects of DEA's timing to establish quotas. For example, manufacturer representatives reported to GAO that the timeline for establishing quotas does not provide manufacturers with enough time to plan for production and order the raw material or API needed to start manufacturing their products at the beginning of the production year. Representatives reported to GAO that they operated solely with what is left in their inventory for the first few months of the production year, "which may be limited because manufacturers operate in a lean manufacturing environment where they carry as little inventory as possible." (Draft, p. 30). This statement from manufacturers is conflicting. Manufacturers complained that they do not have sufficient inventory because of quota and must operate on what is solely remaining in inventory, but then go on to state their business choice to operate in a lean environment where they carry as little inventory as possible. Even so, manufacturers may manufacture API and procure raw material at any time during the year, and not distribute it until the next calendar year because DEA regulations provide for an inventory allowance.

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In addition, a review of ARCOS data would have been critical to determining whether the DEA's processing of supplemental quota applications in 2011 caused or exacerbated FDA-reported drug shortages, as alleged by manufacturers. (Draft, p. 30-31). GAO's probability sample of YERS/QMS source documents showed that it took DEA an average of 58 days to respond to supplemental quota applications in 2011 and 2012. (Draft, p. 30-31). GAO also reported that it took DEA 10 days longer, on average, to respond to supplemental quota applications submitted by manufacturers that reported shortages caused by quota in 2011. However, as discussed above, a review of ARCOS and YERS/QMS information would have established that amphetamine manufacturers only sought authorization to manufacture a very small percentage of the mid-year increase.

Method of Data Analysis:

The report's extensive description of the nature and magnitude of shortages (Draft, p. 17) is misleading as it uses a very broad definition of "shortage," using data from two different sources to quantify and explain the consequences of shortages, and then ties these consequences to the very small number of schedule II drug product "shortages" without ever establishing causation between the specific shortage and the quotas for the specific basic class of controlled substance.

GAO found that approximately 10% (168 of 1,575) of the UUDIS shortages from January 2001 through June 2013 involved drug products containing a controlled substance (Draft, p. 17); of these, 57% (96) involved drug products containing schedule II controlled substances (Draft, p. 19), or approximately 6% (96 of 1,575) of the total number of UUDIS shortages. Because UUDIS information is presented according to NDC rather than the basic class, the results (96 shortages of schedule II controlled substances from 2001 to 2013) can dramatically distort the actual number of shortages that could have been attributed to lack of quota in a particular basic class of controlled substance. The results can also be misleading because UUDIS counts a shortage as a period of time; as a result, 45 different drugs containing controlled substances were reported to be in shortage multiple times from January 2001 through June 2013, representing 143 individual shortages. (Draft, p. 19). The data could also be distorted by the fact that GAO analyzed data from YERS/QMS for 2011 and 2012, rather than 2001 to 2013. Analyzing the information regarding the specific drug products and the specific basic class of controlled substance represented by the 96 NDCs, as well as the calendar year that the substances were reported in shortage would have helped to determine the role, if any, that quota played in any shortage.

GAO also reported that critical shortages represented 52% (87 of 168) of all shortages of drugs containing controlled substances. (Draft, p. 4, n.6; p. 21). Of the 87 shortages containing controlled substances identified as critical by UUDIS from January 2001 through June 2013, half (44 of 87) involved pain relievers (analgesics). (Draft, p. 20-21). Analgesics can be controlled in schedule II, III, IV, or V. However, GAO does not state whether these products contained schedule II controlled substances subject to quota, or schedule III through V controlled substances not subject to quota. This information, along with the NDCs and basic class of controlled substance involved, would be important in determining the role, if any, quota played in any shortage, particularly with respect to the UUDIS "critical shortages," because the applicable criteria (alternative medications are unavailable, the shortages affect multiple manufacturers, or the shortages are widely reported) are more likely to implicate quota than a standard shortage (a supply issue that affects how pharmacies

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prepare and dispense a product or that influences patient care when prescribers must choose an alternative therapy because of a supply issue).

Even so, for the period January 2010 to June 2013, GAO reported that there were 40 FDA-reported shortages of drug products containing schedule II controlled substances, and of those, only seven were alleged to have been caused or exacerbated by quotas. (Draft, p. 30). The remaining 33 reported shortages of drugs containing schedule II controlled substances were caused by other factors that cause shortages of drugs generally such as manufacturing delays, capacity issues, and product quality issues. (Draft, p.30). GAO does not state whether any of these seven shortages occurred during the period in review, 2011 and 2012, nor does GAO indicate which basic class of controlled substance was involved, or whether each shortage involved a different basic class of controlled substance or if a single basic class of controlled substance was involved in several reported shortages. However, GAO contacted the 10 manufacturers that reported the seven shortages from January 2010 to June 2013, and reported that “many” manufacturers stated DEA’s lack of timeliness in establishing quotas caused or exacerbated shortages of their drug products. It does not appear that GAO verified these statements with the data it obtained from YERS/QMS or ARCOS. Rather, the cause of these self-reported shortages was substantiated by collecting anecdotal information from manufacturers.

Some drug products specifically mentioned in the report were in shortage due to reasons other than quota. For example, beginning in 2010, a major manufacturer of injectable drug products containing controlled substances voluntarily shut down certain of its production lines and slowed the release of products in certain manufacturing facilities as a result of certain quality issues cited by the FDA. Such interruptions adversely impacted, and continue to adversely impact, the manufacturer’s ability to manufacture and sell its products. The availability of all injectables were adversely affected, including substances specifically mentioned in the GAO report as having significant deleterious effects on patient care as a result of shortage, such as fentanyl, hydromorphone, and morphine—all schedule II substances subject to quota. Review of the quota data would have shown that when new manufacturers submitted quota applications to meet the new demand, DEA verified with FDA the supply disruption and acted quickly to authorize quota to the new manufacturers.

In addition, some drug products emphasized by GAO when it reported the effects of drug shortages on treatment and patient care were not drug products subject to quota. For example, GAO references an American Society of Anesthesiologists’ survey regarding the effects of drug shortages on anesthesiologists. (Draft, p.24, n.49). The highest frequency of reported shortages were fentanyl (66%), thiopental (40%), succinylcholine (21%), propofol (19%), and pancuronium (15%). As discussed above, fentanyl shortages were due to manufacturing issues. Thiopental is a schedule III controlled substance and thus not subject to quotas; and the remaining three substances are non-controlled substances. In another example, lorazepam injection is a schedule IV controlled substance, and GAO highlighted the adverse consequences of its shortage, indicating that a single shortage of it lasted slightly more than 5 years. (Draft, p. 18). Another consideration GAO ignores is that the benzodiazepines are primarily imported and not manufactured in the United States. Finally, GAO reports that oxycodone oral solution (Draft, p.19), a drug GAO reports is used to treat moderate to severe pain, was in shortage for the longest combined amount of time from January 2001 through June 2013. However, certain oxycodone oral solution drug products were not FDA-approved drugs and could not be lawfully manufactured or distributed until FDA approval in

Joseph T. Rannazzisi, Deputy Assistant Administrator

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September, 2014.

GAO Conclusions:

Failure to utilize the available information as discussed above, and failure to evaluate and analyze the causes of specific controlled substance shortages lead to an analysis that unfairly linked the quota process to diminished patient care. Even though GAO could not find that shortages occurred because of a lack of quota or because of DEA's administration of the quota process, GAO makes several inferences about a relationship between drug shortages and the quota process. This was accomplished because GAO begins its report with identifying trends in shortages from January 2001 through June 2013, and then examines DEA's administration of the quota process, thereby suggesting the effect of the quota process on shortages. However, GAO only evaluated quota data for 2011 and 2012, and its evaluation is not generalizable to other years.

As discussed above, only seven of 40 FDA-reported shortages of drug products containing schedule II controlled substances were alleged to have been caused or exacerbated by quotas. GAO reports that it cannot confirm that DEA's lack of timeliness caused or exacerbated shortages. However, the tools were available to GAO to refute the specific claims that DEA's administration of the quota process caused or exacerbated shortages.

DEA is confident that its administration of the quota process did not affect a shortage during the period in review because drug product shortages are not limited to products that contain schedule II controlled substances. In fact, for the period January 2010 to June 2013, only 18% (7 of 40) of FDA-reported schedule II drug product shortages implicated quotas. Also, UUDIS data shows that from January 2001 through June 2013, approximately 43% of all reported controlled substance shortages were present in schedule III through V drug products, where quotas are not involved. (Draft, p. 19). In addition, GAO found that, from January 2001 through June 2013, the number of new controlled substance shortages reported each year peaked in 2009 and then declined. (Draft, p. 17-18; fig. 2). The increase in these shortages mimics the pattern found for shortages of all drugs, indicating that the same factors affecting shortages of all drugs are also the same factors affecting shortages of drugs containing controlled substances. It is more likely that a common denominator (or a combination of common denominators) are effecting the similar patterns in shortages amongst controlled substances and non-controlled substances; as well as amongst schedule II controlled substances and schedule III through V controlled substances.

GAO concluded that by not acting "promptly" on supplemental applications, DEA may hinder manufacturers' ability to manufacture schedule II drugs that may help prevent or resolve a shortage. However, as explained above, even if DEA increased the APQ or authorized additional manufacturing or procurement quota, manufacturers must apply for it and actually use it to manufacture the drug products in shortage, and then distribute those products downstream—activities that DEA cannot compel.

DEA Response to Recommendations:

GAO Recommendation (1): Establish controls, such as periodic data checks, to ensure that the YERS/QMS data accurately reflect both manufacturers' quota submissions and DEA's decisions.

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Response: The GAO report found that the data error rate was substantially improved from the initial year the process became electronic to the second year (2011 to 2012), dropping from 45% to 10%. (Draft, p. 35). DEA has established policies and procedures to ensure data is accurate. In order to determine the timeliness of responses to submitted requests, there are a number of computer-generated dates, including date submitted, date assigned for review, and date review complete. In order to determine accuracy in quota values being requested and granted there are a series of system-generated flags in YERS/QMS. The flags guide and verify data provided by applicants; and there are flags for internal review, including when a quantity greater than requested is entered. Managers review worksheets for accuracy in summarizing the analysis of the data and supporting documentation provided by the applicant. They then verify that the values contained in the working documents are accurately entered into YERS/QMS. Upon final authorization, managers close the application in YERS/QMS after ensuring that the dates mailed are entered as the authorization letters are scanned and sent to the applicant (via email and U.S. Postal mail). YERS/QMS has a flag to ensure that the date entered is correct.

GAO Recommendation (2): Establish performance measures for DEA related to quotas and ensuring an adequate and uninterrupted supply of controlled substances for legitimate medical use.

Response: DEA recognizes the value in establishing performance measures for personnel reviewing quota applications and will determine whether performance is measurable with regard to processing quotas. Many factors determine how quickly and how accurately a quota application is reviewed and a quota recommended. For example, a single quota application is for one specific basic class; however, each quota request may involve quota for more than one specific drug product containing that basic class. The reasonable amount of time to evaluate each application is highly dependent on how many different factors affect a single request.

GAO Recommendation (3): Monitor and analyze YERS/QMS data to assess DEA's administration of the quota process.

Response: DEA agrees that monitoring and analyzing YERS/QMS data is important to ensuring proper administration of the quota process. The YERS/QMS data are integrally related for manufacturing and procurement quotas applications and responses. The data are reviewed and monitored constantly when analyzing each quota application. For example, with the APQ set as the maximum of each basic class to be manufactured each year, the quota review process of every manufacturing quota application checks the APQ, amounts issued, pending and remaining. In addition, the manufacturing quota data are analyzed and used with other sources to establish and revise the annual APQs.

GAO Recommendation (4): Establish internal policies for processing quota applications and setting aggregate, annual, and supplemental quotas to ensure that staff conduct these activities consistently and in accordance with the CSA and agency's regulations.

Response: DEA has established policies and procedures for staff administering the quota

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procedures. In addition, beginning with 2013 APQs, DEA included an additional 25% of the estimated medical, scientific, and research needs as part of the amount necessary to ensure the establishment and maintenance of reserve stocks. DEA expects that maintaining this reserve in the aggregate production quotas will mitigate adverse public affects if an unforeseen event results in substantial disruption to the amount of controlled substances available to provide for legitimate public need.

GAO Recommendation (5): Expeditiously establish formal policies and procedures to facilitate coordination with FDA as directed by FDASIA, including a specific timeframe in which DEA will be expected to respond to FDA requests to expedite shortage-related quota applications.

Response: DEA shall follow the requirements of FDASIA to respond to requests within 30 days. It should be noted that no special requests for expedited quota review have been forwarded to DEA since enactment of FDASIA in July, 2012. As previously conveyed to GAO, DEA and FDA began negotiating the terms of a new information sharing agreement before this engagement commenced. As of December 15, 2014, the final memorandum of agreement has been routed for signature within DEA.

GAO Recommendation (6): Promptly update the MOU between the two agencies.

Response: As previously conveyed to GAO, DEA and FDA began negotiating the terms of a new information sharing agreement before this engagement commenced. As of December 15, 2014, the final memorandum of agreement has been routed for signature within DEA.

GAO Recommendation (7): Either in the MOU or in a separate agreement, specifically outline what information the agencies will share, and timeframes for sharing such information, in response to a potential or existing drug shortage.

Response: As previously conveyed to GAO, DEA and FDA began negotiating the terms of a new information sharing agreement before this engagement commenced. As of December 15, 2014, the final memorandum of agreement has been routed for signature within DEA. DEA and FDA have engaged in discussions to determine the specific procedures by which information regarding drug shortages shall be exchanged, pursuant to FDASIA. These procedures will be memorialized in a mutually agreeable workplan.

Conclusion:

There can be no doubt that drug shortages adversely affect the public health. Drug shortages occur across the continuum of pharmaceutical characteristics, e.g., brand, generic, controlled, non-controlled, over-the-counter, dosage forms and dosage strengths, analgesics, sedatives, stimulants. Shortages can be caused by a variety of factors, as GAO previously reported in 2011 and 2014. Determining the relationship between retail and EMS level drug product shortages and manufacturing quota is a multifaceted undertaking that particularly requires an understanding of controlled substance manufacturing and distribution practices, an appreciation of how competitive contractual agreements affect the actions of manufacturers, distributors, and patent owners, and how

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these dynamics influence the annual forecasting of quota need.

DEA remains committed to establishing production quotas for each basic class of controlled substance in schedule II to be manufactured each year to provide for the estimated medical, scientific, research, and industrial needs of the United States, for lawful export requirements, and for the establishment and maintenance of reserve stocks. Accordingly, DEA appreciates the GAO finding that it cannot establish a causal relationship between shortages of drugs containing controlled substances and DEA's management of the quota setting process.

Should you have any questions regarding this matter or our comments, please contact Michael A. Dixon, Acting Deputy Chief Inspector, Office of Inspections, at (202) 307-4007.

Sincerely,



Joseph T. Rannazzisi
Deputy Assistant Administrator
Office of Diversion Control

cc: Richard P. Theis
Director, Audit Liaison Group
Internal Review and Evaluation Office
Justice Management Division

Appendix VI: GAO Contact and Staff Acknowledgments

GAO Contact

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

Staff Acknowledgments

In addition to the contact named above, Geri Redican-Bigott, Assistant Director; Zhi Boon; Jessica Farb; Cathleen Hamann; Rebecca Hendrickson; Tom Jessor; Eileen Larence; Jan Montgomery; Lisa Motley; Leslie Powell; Dan Ries; Janet Temko-Blinder; Sonya Vartivarian; and Eric Wedum made key contributions to this report.

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