



February 2014

DRUG SHORTAGES

Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability

GAO Highlights

Highlights of [GAO-14-194](#), a report to congressional addressees

Why GAO Did This Study

From prolonged duration of a disease, to permanent injury, to death, drug shortages have led to harmful patient outcomes. FDA—an agency within the Department of Health and Human Services (HHS)—is responsible for protecting public health and works to prevent, alleviate, and resolve shortages. In 2011, GAO recommended that FDA should enhance its ability to respond to shortages. In 2012, FDASIA gave FDA new authorities to improve its responsiveness and mandated GAO to study drug shortages.

In this report, GAO (1) reviews the trends in recent drug shortages and describes what is known about their effect on patients and providers; (2) examines the causes of drug shortages; and (3) evaluates the progress FDA has made in addressing drug shortages. GAO analyzed data from FDA and the University of Utah Drug Information Service, which is generally regarded as the most comprehensive source of drug shortage information for the time period we reviewed. GAO interviewed officials from FDA and other federal agencies, organizations representing patients and providers, and drug manufacturers. GAO also reviewed the literature, relevant statutes, regulations, and documents.

What GAO Recommends

FDA should strengthen its internal controls over its drug shortage data and conduct periodic analyses to routinely and systematically assess drug shortage information, using this information to proactively identify drug shortage risk factors. HHS agreed with GAO's recommendations.

View [GAO-14-194](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

February 2014

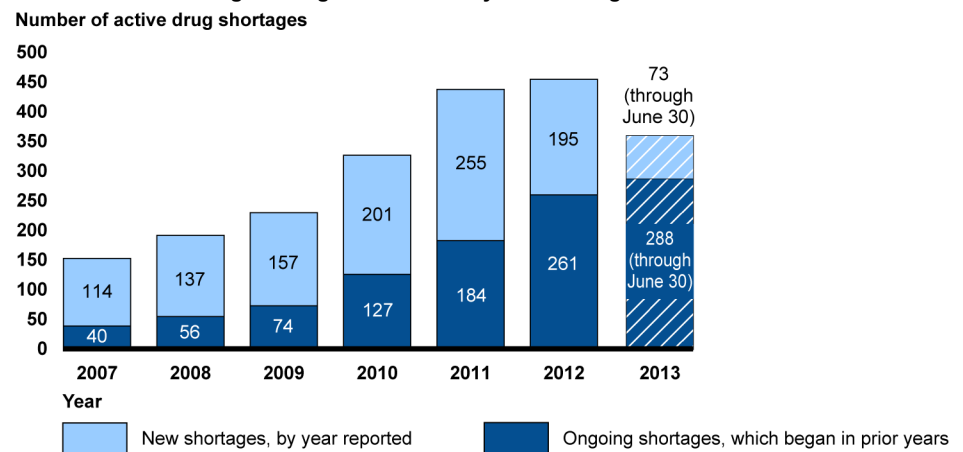
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Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability

What GAO Found

The number of drug shortages remains high. Although reports of new drug shortages declined in 2012, the total number of shortages active during a given year—including both new shortages reported and ongoing shortages that began in a prior year—has increased since 2007. Many shortages are of generic sterile injectable drugs. Provider association representatives reported that drug shortages may force providers to ration care or rely on less effective drugs.

Number of Active Drug Shortages from January 2007 through June 2013



Source: GAO analysis of University of Utah Drug Information Service data.

The immediate cause of drug shortages can generally be traced to a manufacturer halting or slowing production to address quality problems, triggering a supply disruption. Other manufacturers have a limited ability to respond to supply disruptions due to constrained manufacturing capacity. GAO's analysis of data from the Food and Drug Administration (FDA) also showed that quality problems were a frequent cause. GAO also identified potential underlying causes specific to the economics of the generic sterile injectable drug market, such as that low profit margins have limited infrastructure investments or led some manufacturers to exit the market.

While shortages have persisted, FDA has prevented more potential shortages in the last 2 years by improving its responsiveness. Among other things, FDA implemented Food and Drug Administration Safety and Innovation Act (FDASIA) requirements and recommendations GAO made in 2011. FDA has also initiated other steps to improve its response to shortages, such as developing procedures to enhance coordination between headquarters and field staff. However, there are shortcomings in its management of drug shortage data that are inconsistent with internal control standards. For example, FDA has not created policies or procedures governing the management of the data and does not perform routine quality checks on its data. Such shortcomings could ultimately hinder FDA's efforts to understand the causes of specific shortages as well as undermine its efforts to prevent them from occurring. In addition, FDA has not conducted routine analyses of the data to proactively identify and evaluate the risks of drug shortages.

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Abbreviations

ANDA	abbreviated new drug application
API	active pharmaceutical ingredient
CDER	Center for Drug Evaluation and Research
CGMP	Current Good Manufacturing Practice
DEA	Drug Enforcement Administration
DOJ	Department of Justice
DSS	Drug Shortage Staff
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FDCA	Federal Food, Drug, and Cosmetic Act
FTC	Federal Trade Commission
GPO	group purchasing organization
HCPCS	Healthcare Common Procedure Coding System
HHS	Department of Health and Human Services
NDA	new drug application
NDC	national drug code
UUDIS	University of Utah Drug Information Service

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February 10, 2014

Congressional Addressees

From prolonged duration of a disease, to permanent injury, to death, drug shortages have led to harmful outcomes for patients of all ages. Over the last decade, an increasing number of prescription drugs—including life-saving and life-sustaining drugs—have been in short supply, preventing health care providers and patients from accessing medications that are essential for treatment. During shortages, providers—including hospitals, physicians, and pharmacists—may have to use medications that could be less effective for treating conditions or carry unwanted side-effects, if alternatives are available at all.

The Food and Drug Administration (FDA)—an agency within the Department of Health and Human Services (HHS)—is responsible for overseeing the safety and effectiveness of drugs marketed in the United States, including addressing drug shortages. A unit within FDA, referred to as the Drug Shortage Staff (DSS), coordinates the agency's activities to prevent, alleviate, and resolve shortages. FDA defines 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. In November 2011, we reported on the growing number of drug shortages and their causes and found that the agency lacked sufficient authority to respond to shortages. We recommended that FDA strengthen its response and suggested that Congress consider establishing a requirement for manufacturers to report potential or actual supply disruptions to FDA.¹

The Food and Drug Administration Safety and Innovation Act (FDASIA), enacted in July 2012, provided FDA new authorities to address drug shortages.² It also assigned the agency new responsibilities. Further, FDASIA mandated us to examine several different aspects of shortages including their characteristics and causes, the effect on providers, and

¹GAO, *Drug Shortages: FDA's Ability to Respond Should be Strengthened*, [GAO-12-116](#) (Washington, D.C.: Nov. 21, 2011).

²Pub. L. No. 112-144, 126 Stat. 993 (2012).

FDA's role in resolving them, among other things.³ This report (1) reviews the trends in recent drug shortages and describes what is known about their effect on patients and providers, (2) examines the causes of drug shortages, and (3) evaluates the progress FDA has made in addressing drug shortages.

To review the trends in recent drug shortages, we analyzed data from the University of Utah Drug Information Service (UUDIS) on drugs that were in short supply from January 1, 2007, through June 30, 2013, which were the most recent data available at the time we did our work.⁴ These data are generally regarded as the most comprehensive and reliable source of drug shortage information for the time period we reviewed and are what we used in preparing our 2011 report.⁵ We also examined the characteristics of 219 of these drugs that were reported to be in shortage at some point between June 1, 2011, and June 30, 2013, and that UUDIS

³In addition to the FDASIA mandate that we report on drug shortages, members of the Senate Judiciary Committee have requested that we conduct an examination specifically related to the shortages of controlled substances. As a result, issues unique to controlled substances are not specifically discussed in this report.

⁴Our 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. 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 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.

⁵[GAO-12-116](#), 2. At the time of our previous report, FDA did not have a database containing information on drug shortages for the time period we reviewed. Since the publication of that report, FDA has developed a database that it uses to track shortages. For the purposes of this report, we used the drug shortage data maintained by UUDIS because the time period we reviewed included data from years that predate FDA's development of its database and to provide comparable information on the trends and characteristics of drug shortages to that which we presented in our 2011 report. In that report, we analyzed UUDIS data on the number of drug shortages reported between January 1, 2001, and June 20, 2011.

identified as critical because alternative medications were unavailable, the shortages affected multiple manufacturers, or it received multiple reports from different institutions.⁶ These 219 critical shortages were a subset of the total number of shortages reported during this time.⁷ For this subset of shortages, we identified their product types, routes of administration, and therapeutic classes. We reviewed all UUDIS data used for reasonableness, outliers, and consistency, and based on our review, determined that the data were sufficiently reliable for our purposes. To describe the effect of drug shortages on patients and providers, we interviewed representatives from 10 national associations representing health care providers including physicians, hospitals, and pharmacists.⁸ We asked these stakeholders a series of open-ended questions and did not independently validate their responses. We also reviewed relevant documents from the various organizations, including surveys, congressional testimony, and comments submitted to FDA related to drug shortages.⁹

To examine the causes of recent drug shortages we performed a search of research databases to identify any literature published from January 1, 2003, through June 30, 2013, that reported on the causes of drug shortages. We identified and reviewed 20 studies, which included journal articles, working papers, and government publications that either presented original research on the causes of drug shortages or included an in-depth discussion of the causes of drug shortages. We also interviewed drug manufacturers to obtain their views about the causes of drug shortages. Finally, we analyzed FDA data on the reported causes of shortages that occurred from January 1, 2011, through June 30, 2013.¹⁰

⁶In our 2011 report, we examined the characteristics of critical drug shortages identified between January 1, 2009, and June 20, 2011. [GAO-12-116](#), 2.

⁷These 219 shortages represented 57 percent of the 382 shortages reported from June 2011 through June 2013.

⁸We also interviewed officials from five federal agencies that are major purchasers of prescription drugs—the Department of Defense, the Department of Veterans Affairs, the U.S. Coast Guard, the National Institutes of Health, and the Indian Health Service—to obtain information on how shortages may affect federal spending.

⁹In February 2013, FDA published a Notice in the Federal Register with a request for comment about its drug shortages task force and strategic plan. 78 Fed. Reg. 9928 (Feb. 12, 2013).

¹⁰FDA did not have data readily available on the reported causes of shortages that began prior to January 1, 2011.

We reviewed all FDA data used for reasonableness, outliers, and consistency, and based on our review, determined that the data were sufficiently reliable for our purposes.

To evaluate the progress FDA has made in responding to drug shortages, we reviewed documentation and interviewed FDA officials regarding the agency's current approach to managing drug shortages and implementing FDASIA requirements. This included reviewing FDA data related to drug shortages, including information contained in its recently created drug shortages database and information about shortages published on its website. We also analyzed FDA information on potential drug shortages the agency prevented from January 2011 through June 2013. To determine the number of shortages prevented, we grouped together shortages that involved multiple versions of a drug that had the same route of administration. We compared FDA's drug shortage management activities to the relevant standards described in the *Standards for Internal Control in the Federal Government* and to the agency's requirements under FDASIA.¹¹ We also interviewed relevant market participants, such as manufacturers and provider groups, to obtain their perspective on the recent steps that FDA has taken to address shortages and the effectiveness of FDA's efforts to prevent, mitigate, and resolve drug shortages.

Appendix I contains additional information on the methodology we used to describe the trends in and causes of drug shortages and the steps we took to determine the reliability of the data we used. Appendix II contains a complete list of the federal agencies and other stakeholders we interviewed for this report.

We conducted this performance audit from January 2013 to February 2014 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

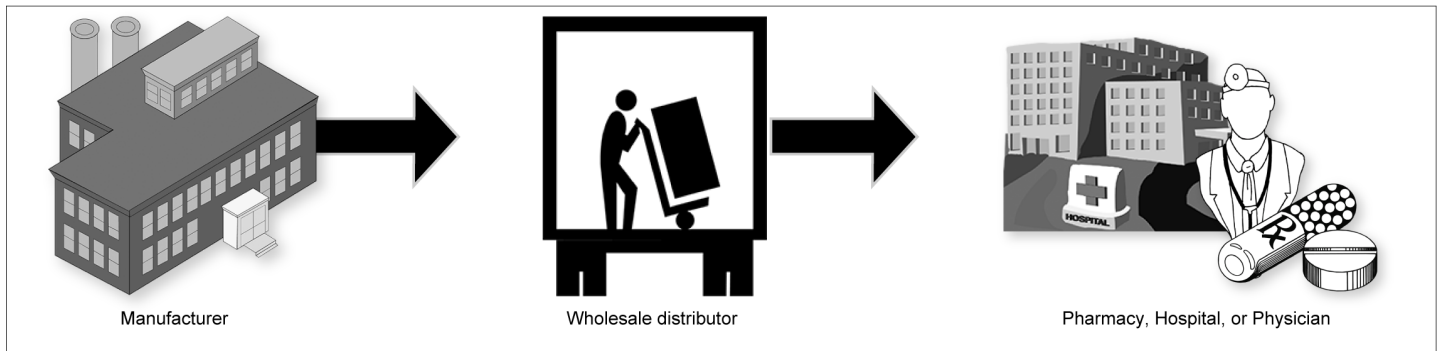
¹¹See GAO, *Standards for Internal Control in the Federal Government*, [GAO/AIMD-00-21.3.1](#) (Washington, D.C.: November 1999).

Background

Drug Shortages

Many participants along the entire drug supply chain are affected by shortages. A typical drug supply chain involves a drug manufacturer selling a drug to a wholesale distributor, which then sells the drug to a hospital or pharmacy. (See fig. 1.)

Figure 1: Key Drug Supply Chain Participants Affected by Drug Shortages



Sources: GAO; Art Explosion (images).

Shortages of drugs can result in a variety of problems that directly affect the care patients receive. For example, recent research on the effects of drug shortages identified an increase in adverse outcomes among pediatric cancer patients treated with an alternative drug.¹² Further, in some cases, drug shortages can even contribute to additional health problems. For example, one stakeholder said that recent shortages of drugs that supply an essential nutrient, like calcium, could lead to nutrient deficiencies among patients.

¹²Estimated 2-year cancer-free survival for children with Hodgkin's lymphoma treated by members of the Pediatric Hodgkin Lymphoma Consortium fell from 88 to 75 percent after the drug cyclophosphamide was substituted for mechlorethamine, when the latter was in shortage. The researchers concluded that there was no credible explanation for this decline other than the drug substitution. M. L. Metzger, A. Billett, and M. P. Link, "The Impact of Drug Shortages on Children with Cancer—The Example of Mechlorethamine," *New England Journal of Medicine*, vol. 367, no. 26 (2012).

FDA Oversight of Drugs

FDA is responsible for overseeing the safety and effectiveness of drugs marketed in the United States. Within FDA, the Center for Drug Evaluation and Research (CDER) manages these responsibilities. FDA's approval is required before new drugs and generic drugs can be marketed for sale.¹³ To obtain FDA's approval for a new drug, sponsors must submit a new drug application (NDA) containing data on the safety and effectiveness of the drug as determined through clinical trials and other research for review by CDER's Office of New Drugs. Sponsors of generic drugs may obtain FDA approval by submitting an abbreviated new drug application (ANDA) to the agency for review by CDER's Office of Generic Drugs. The ANDA must contain data showing, among other things, that the generic drug is bioequivalent to, or performs in the same manner as, a drug approved through the NDA process.¹⁴ After obtaining FDA's approval, drug companies that want to change any part of their original application—such as changes to product manufacturing location or process, type or source of active ingredients, or the product's labeling—must generally submit an application supplement to notify FDA of the change and, if the change has a substantial potential to have an adverse effect on the product, obtain FDA's approval.¹⁵

After approving new and generic drugs for marketing, FDA's responsibilities continue as it is charged with monitoring the safety, effectiveness, quality, and promotion of approved drugs, and the agency may take enforcement actions in response to violations of law and regulations. For example, as part of its efforts to ensure the safety of approved drugs, FDA periodically inspects drug manufacturing establishments to assess their ongoing compliance with Current Good Manufacturing Practice (CGMP) regulations.¹⁶ If FDA identifies a violation of law or regulations, it may issue a warning letter or take an enforcement

¹³21 U.S.C. § 355.

¹⁴21 U.S.C. § 355(j). The application for generic drugs is abbreviated because FDA does not require sponsors to conduct, or provide evidence from, clinical trials that are required of sponsors of new drugs.

¹⁵21 C.F.R. §§ 314.70, 314.97 (2013). Specifically, any change that has a substantial potential to adversely affect factors such as the identity, strength, quality, purity, or potency of a drug product requires FDA review and approval of a "prior approval" supplement before a drug manufactured using this change can be distributed.

¹⁶CGMP regulations provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210-211.

action. In some cases, FDA may exercise its regulatory discretion and assess whether the risks of either taking a certain enforcement or other action or refraining from taking action will outweigh the benefits, such as when an action may cause or exacerbate a drug shortage.¹⁷ For example, if a manufacturing deficiency is identified, such as overfilled vials or the presence of contaminants, the manufacturer should take appropriate corrective and preventive actions, or FDA may issue a warning letter or take an enforcement action to require the manufacturer to do so. Similarly, FDA may request manufacturers of drugs whose labeling is not consistent with the labeling approved by FDA to correct such labeling, or it may take an regulatory action to require the manufacturers to do so.

FDA Role in Resolving Drug Shortages

In 1999, FDA established the CDER Drug Shortage Program—now known as DSS—to coordinate issues related to drug shortages.¹⁸ Once DSS determines that a shortage is in effect or a potential shortage is pending, it contacts manufacturers of the drug to collect up to date information on inventory of the drug, demand for the drug, and manufacturing schedules. DSS may also coordinate its response with several offices including the Office of Generic Drugs, Office of New Drug Quality Assessment, and CDER’s Office of Compliance—the office responsible for minimizing consumer exposure to unsafe, ineffective, and poor quality drugs. DSS may also work with FDA’s Office of Regulatory Affairs—the office within FDA that oversees imports, inspections, and enforcement policy—and the manufacturer to help resolve any underlying problem a manufacturer is facing. If the shortage is of a controlled

¹⁷In determining how to respond to a shortage, FDA takes steps to determine whether a drug is medically necessary, defined as any drug that is used to treat or prevent a serious disease or medical condition for which there is no other adequately available drug that is judged by medical staff to be an appropriate substitute. Officials previously told us that they do not typically consider exercising regulatory discretion to respond to shortages of non-medically necessary drugs because these drugs are, by definition, not used to treat serious diseases or medical conditions, or other clinically interchangeable versions of the drug are available.

¹⁸The Drug Shortage Program became known as DSS when CDER elevated it from the Office of New Drugs to the Immediate Office of the Center Director within CDER.

substance, FDA may work with the Drug Enforcement Administration (DEA) on any issues related to quotas for the production of the drug.¹⁹

When FDA is informed of a potential shortage in advance, it may take steps to prevent the shortage, such as providing assistance to address manufacturing problems.²⁰ For example, it may offer feedback on a manufacturer's proposed approach to responding to quality concerns. In addition, FDA can expedite inspections of manufacturing establishments to facilitate the marketing of an alternative to a drug in shortage or can expedite inspections once remediation to address quality problems has been completed.

FDA may also apply its regulatory discretion to enhance the availability of drugs. For example, FDA may refrain from taking regulatory or enforcement action to stop the distribution of a drug that is in shortage if the manufacturer makes the decision to continue marketing the drug despite a labeling or quality issue, effectively allowing the manufacturer to continue marketing the drug.²¹ In doing so, FDA balances the drug's risk to a patient with the risks of the drug not being available. In the event that a shortage cannot be averted, FDA may take other actions to enhance product availability. For example, in certain circumstances, FDA may not object to the temporary importation of drugs not approved by FDA for marketing in the United States, subject to appropriate controls effectively allowing the drugs to be temporarily marketed in the United States.²² Also, FDA can expedite the review of ANDAs, in order to provide

¹⁹Controlled substances have the potential for abuse and are regulated by the DEA in accordance with the Controlled Substances Act. They include narcotics, stimulants, depressants, sedatives, and anabolic steroids. DEA limits the availability of these substances by establishing quotas for the substance that can be produced or procured each year.

²⁰FDA officials said that they take steps to address shortages of both medically necessary drugs and non-medically necessary drugs, though they give priority to shortages of medically necessary drugs.

²¹FDA officials explained that the agency's exercise of regulatory discretion does not mean that these products meet regulatory standards for approval, or that a manufacturer has a legal right to distribute them. Rather, FDA may decide not to object to the distribution of the drug for a limited time for public health reasons.

²²FDA officials said they may also identify other alternative sources of drugs, some of which may not require importation. For example, a U.S. manufacturer of a drug which is approved for distribution in Canada may be allowed to temporarily market the drug in the United States, in response to a drug shortage.

additional sources of a drug in shortage, or supplements to ANDAs or NDAs, to provide additional capacity for production of an already approved drug. While there are a number of steps FDA can take to address a shortage, FDA cannot require manufacturers to start producing or continue to produce a drug. It also cannot require manufacturers to maintain or introduce manufacturing redundancies in their establishments to provide them with increased flexibility to respond to shortages.

On October 31, 2011, the President issued an Executive Order that directed FDA to use its authority to encourage manufacturers to report drug supply disruptions earlier, to expedite regulatory review, when possible, to prevent or mitigate drug shortages, and to communicate to the Department of Justice any findings by FDA that shortages have led market participants to stockpile shortage drugs or sell them at exorbitant prices.²³

In November 2011, we found that weaknesses in FDA's ability to respond resulted in a predominately reactive approach to addressing shortages, although this was partially due to the fact that, at the time our report was issued, FDA did not have the authority to require manufacturers to notify the agency of most impending shortages.²⁴ Our previous report contained several recommendations for FDA, including assessing the resources that FDA allocates to its DSS; developing an information system to manage data on shortages; ensuring that FDA's strategic plan articulates goals and priorities for maintaining the availability of drugs; and developing results-oriented performance metrics related to FDA's response to drug shortages.²⁵ FDA outlined actions it planned to take which were consistent with these recommendations.

Subsequently, the enactment of FDASIA in July 2012 resulted in several new requirements for FDA and manufacturers intended to address drug shortages. (See table 1 for a summary of these provisions.)

²³Exec. Order No. 13,588 reprinted at 3 C.F.R. 281 (2012).

²⁴[GAO-12-116](#), 35. At the time, FDA's sole authority over manufacturers' reporting of drug shortages pertained to the discontinuation of approved drugs that were life-supporting, life-sustaining, or for use in the prevention of a debilitating disease or condition, when such drugs were produced by only one manufacturer.

²⁵[GAO-12-116](#), 43-44.

Table 1: FDA Related Drug Shortage Provisions Enacted under Title X of the Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144

Provision	Description
Task Force and Strategic Plan	FDA must establish a task force to develop and implement a strategic plan for enhancing FDA's response to preventing and mitigating drug shortages. The law directed the task force to publish and submit the strategic plan to Congress by July 9, 2013.
Manufacturer Notice	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 notice is not feasible) in the manufacture of a drug that is life supporting, life sustaining, or used to treat debilitating health issues. Failure to do so will result in a letter from FDA to which the company must reply within 30 days. If compliance does not occur within 45 days of FDA's letter, the agency is required to post its letter and any response from the manufacturer on the FDA website. FDASIA required FDA to adopt regulations implementing these requirements by January 9, 2014.
Coordination and Communication	FDA is to identify whether a given enforcement action or warning letter could cause or exacerbate a drug shortage prior to taking the enforcement action or sending the warning letter [a warning letter notifies any responsible individual or firm that the agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (FDCA), related regulations, or other federal statutes]. If so, FDA is to evaluate the risks of the drug shortage and the risks associated with the violation before taking the action or issuing the letter, unless there is an imminent risk of serious adverse health consequences or death from not taking the action or issuing the letter.
Expediting FDA Actions	In response to a pending or active shortage, FDA may expedite the review of an abbreviated new drug application (ANDA), or a supplement to either an ANDA or a new drug application that could prevent or mitigate a shortage. FDA may also expedite inspection or reinspection of an establishment to prevent or mitigate a shortage.
Controlled Substances	To address a pending or active shortage of a controlled substance, FDA may, if necessary, notify the Drug Enforcement Administration (DEA) of the shortage and request that the DEA increase the aggregate and individual production quotas for the substance to a level FDA deems necessary to address the shortage. If DEA disagrees, it must provide FDA a written response to be made public on the FDA website explaining the decision.
Annual Report	FDA is required to provide Congress with an annual report that contains a variety of information related to drug shortages, including the number of shortages that occurred that calendar year, manufacturer notifications of potential shortages, FDA actions to prevent or mitigate shortages (including identifying instances where FDA exercised regulatory discretion), communication within FDA, FDA coordination with DEA, and a list of manufacturers that were issued noncompliance letters related to the notification requirement. The first annual report was due by the end of calendar year 2013. FDASIA authorized FDA to retain a third party to conduct a study on drug shortages (specifically the causes, trends, or solutions), in conjunction with the preparation of the annual report.
Shortage Information	FDA must distribute information, to the maximum extent practicable, on the discontinuance or interruption in the manufacture of a drug that is life supporting, life sustaining, or used to treat debilitating health issues to appropriate groups, including physician and patient groups.
Third Party Notification	FDA is required to identify or establish a mechanism for health care providers or other third-party organizations to report evidence of drug shortages to FDA.

Provision	Description
Shortage List	FDA must maintain an up-to-date list of drugs in shortage, which, subject to public health, trade secret, and confidentiality concerns, must be publicly available. For each drug on the list, FDA must identify the reason for shortage using a standard list of reasons for shortages that were included in FDASIA.

Source: GAO analysis of FDASIA.

Note:

^aControlled substances have the potential for abuse and are regulated by the DEA in accordance with the Controlled Substances Act. DEA limits the availability of these substances by establishing quotas for the amount of the substance that can be produced or procured each year.

The Number of Drug Shortages Remains High, Complicating Providers' Ability to Care for Patients

The number of drug shortages remains high, with almost half of critical shortages involving generic sterile injectable drugs. Provider association representatives identified challenges in responding to drug shortages without adversely affecting patient care.

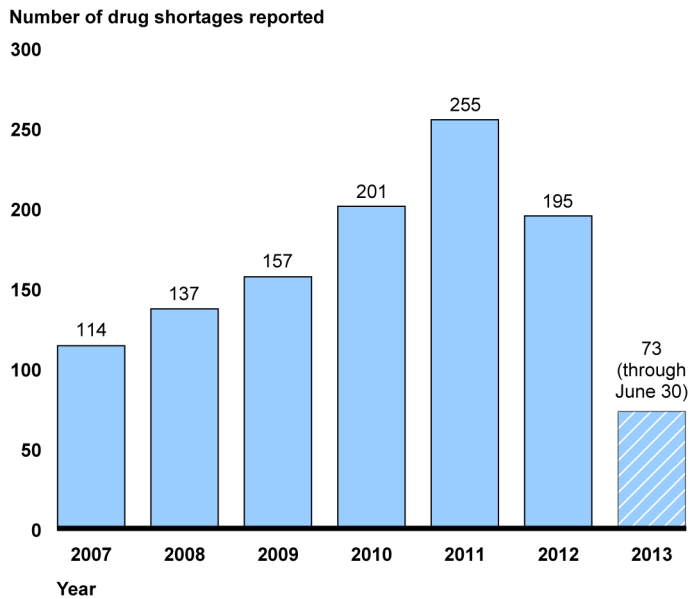
The Number of Drug Shortages Remains High and Nearly Half Involve Generic Sterile Injectables

The number of drug shortages reported each year remains high, although there was a decrease in 2012 relative to the record number of new shortages reported in 2011.²⁶ We found that from 2007 through 2011, the number of drug shortages reported increased each year, with a record 255 shortages reported in 2011.²⁷ However, in 2012, for the first time since 2006, there was a decrease in the number of drug shortages reported. Specifically, in 2012, 195 shortages were reported, which was a 24 percent decrease from 2011. As of June 30, 2013, 73 shortages had been reported in 2013. (See fig. 2.)

²⁶A shortage is only 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 only be counted as a reported shortage in 2010. It would not be counted as a reported shortage in either 2011 or 2012, although it would be counted in the total number of active shortages in each of those years.

²⁷From January 1, 2001, through December 31, 2006, a total of 443 shortages were reported to UUDIS. In 2001, 102 shortages were reported, but there were fewer than 100 shortages reported in each year from 2002 through 2006.

Figure 2: Drug Shortages Reported from January 2007 through June 2013



Source: GAO analysis of University of Utah Drug Information Service data.

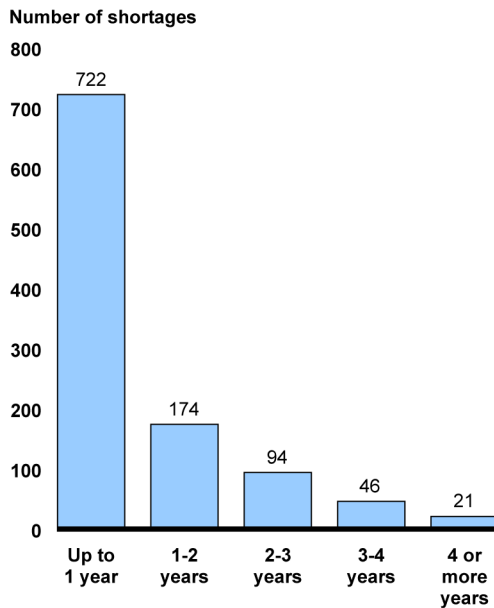
Note: A shortage is counted as “reported” in the year that the University of Utah Drug Information Service is first notified of the shortage. The totals reported for 2007 through 2011 may differ slightly from what we reported in our 2011 report, due to minor modifications by the University of Utah Drug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

Over half (55 percent, or 622) of the 1,132 shortages reported since January 1, 2007, were for drugs that were in shortage more than once. Specifically, 240 drugs were in shortage on multiple occasions between January 1, 2007, and June 30, 2013, representing 622 individual shortages.

For shortages reported since January 1, 2007, the duration of the shortages varied, ranging from 1 day to over 5 years. The majority of shortages—68 percent—lasted 1 year or less.²⁸ The average duration of the drug shortages over this period was 340 days—slightly less than a year. (See fig. 3.)

²⁸We excluded 75 shortages from this analysis because UUDIS listed these shortages as lasting zero days. The majority of these represented manufacturers’ decisions to discontinue their production of a drug.

Figure 3: Distribution of the Duration of Reported Drug Shortages from January 2007 through June 2013



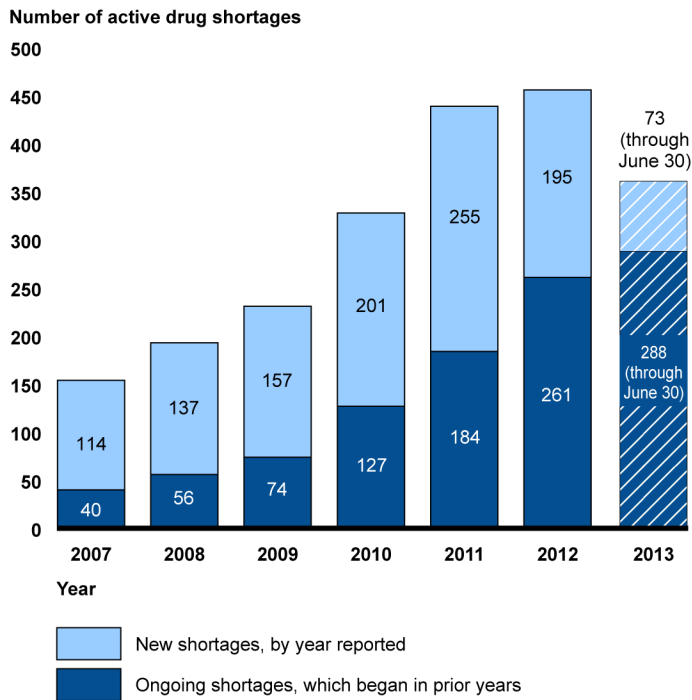
Source: GAO analysis of University of Utah Drug Information Service data.

Note: Our analysis of the duration of shortages includes 1,057 of the 1,132 total shortages reported as new shortages from January 1, 2007, through June 30, 2013; we excluded 75 shortages from this analysis because the University of Utah Drug Information Service listed these shortages as lasting zero days. The majority of these represented manufacturers' decisions to discontinue their production of a drug.

Though the number of shortages reported has recently declined, the number of active shortages remains high. The total number of active shortages each year has increased steadily since 2007.²⁹ Specifically, the number of active shortages each year almost tripled between 2007 and 2012 from 154 in 2007 to 456 in 2012. In 2012, the 456 active shortages were comprised of 195 new shortages and 261 shortages that began before 2012 but remained ongoing for some period of time in 2012. As of June 30, 2013, there had been 361 shortages active in 2013, including 288 ongoing shortages that had started in prior years. (See fig. 4.)

²⁹The 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).

Figure 4: Number of Active Drug Shortages from January 2007 through June 2013



Source: GAO analysis of University of Utah Drug Information Service data.

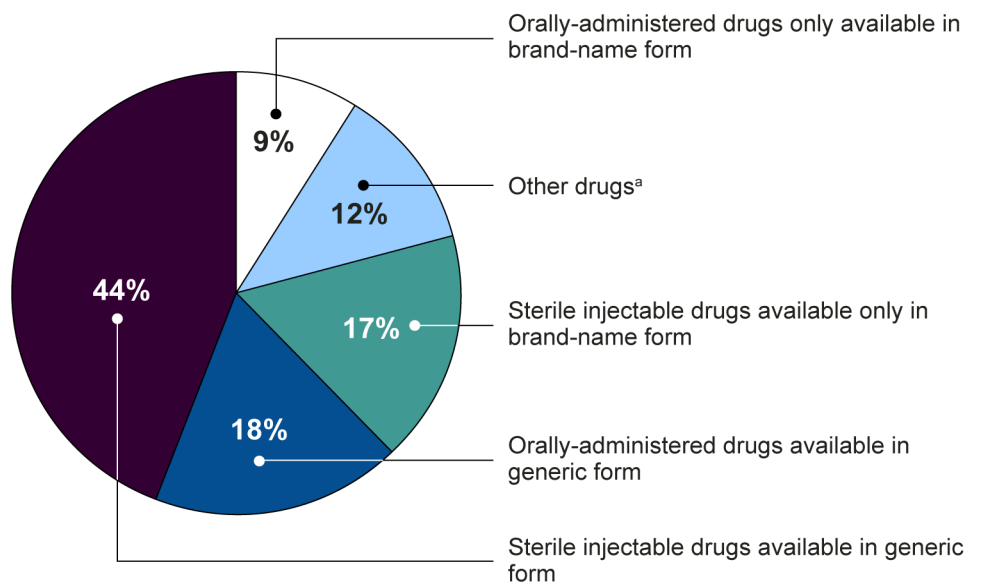
Note: The active shortage total for each year includes (1) new shortages reported that year and (2) shortages that started in a prior year that were still ongoing.

Based on our review of the characteristics of a subset of drug shortages reported between June 1, 2011, and June 30, 2013, that UUDIS identified as critical, we found that 44 percent of the 219 critical shortages involved generic sterile injectable drugs.³⁰ These shortages were identified by UUDIS as critical because alternative medicines were not available, the shortages affected multiple manufacturers, or it received multiple reports from different institutions. Of the 96 shortages that constitute the 44 percent of critical shortages that involved sterile injectables in generic form, 63 shortages were of drugs available only in generic form, while 33 shortages were of drugs that were available in both generic and brand-name form. An additional 17 percent of critical shortages involved sterile

³⁰UUDIS identified 219 of the 382 shortages reported from June 1, 2011, through June 30, 2013 as critical shortages. We reviewed the characteristics of those 219 critical shortages, which represented 57 percent of all shortages reported during this time.

injectables that were available only in brand-name form. The remaining percentage of critical shortages—about 39 percent—involved either generic or brand-name drugs administered either orally or through other routes.³¹ (See fig. 5.)

Figure 5: Distribution of Critical Drug Shortages Reported from June 2011 through June 2013, by Route of Administration and Product Type



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

Notes: This figure reflects 219 of the 382 shortages (57 percent) reported during this time period. Our analysis was 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.

^aOther drugs includes those that had other routes of administration such as, nasal, inhalation, topical, ophthalmic, and transdermal methods. In total, there were 18 drugs available through other routes, with 4 available in generic form and the remaining 14 only available in brand-name form. The Other drugs category also includes 9 additional shortages that had multiple routes of administration or for which either the route of administration or the product type was unavailable from Red Book.

³¹In our November 2011 report, we found that for critical shortages reported between January 1, 2009, and June 20, 2011, 53 percent of the shortages were generic sterile injectable drugs and 15 percent were brand-name sterile injectable drugs. The remaining shortages (32 percent) were shortages of generic and brand-name drugs available through other routes, such as drugs that were orally-administered. See [GAO-12-116](#), 19.

Certain therapeutic classes were more likely to have shortages reported than others. Specifically, four therapeutic classes—anti-infective, anesthetic and central nervous system, cardiovascular, and nutritive—comprised 53 percent of critical drug shortages.³² Anesthetic and central nervous system drugs and anti-infective drugs were the most represented therapeutic classes, with 17 and 16 percent of shortages reported respectively.³³ (See table 2.)

³²Examples of shortages in these therapeutic classes during this time period included, acyclovir and doxycycline (anti-infective); propofol and diazepam (anesthesia and central nervous system); nitroglycerin and verapamil (cardiovascular); and potassium chloride and sodium phosphate (nutritive).

³³We previously found that anesthetic and central nervous system drugs and anti-infective drugs were among the therapeutic classes with the most shortages reported between January 1, 2009, and June 20, 2011. Previously, 23 percent of shortages were anesthetic and central nervous system drugs and 14 percent of shortages were anti-infective drugs. See [GAO-12-116](#), 21.

Table 2: Summary of Critical Drug Shortages Reported from June 2011 through June 2013, by Therapeutic Class

Therapeutic Class	Number of Critical Shortages	Percent of Critical Shortages
Anesthetic and central nervous system drugs	37	17
Anti-infective drugs	34	16
Cardiovascular drugs	27	12
Nutritive drugs	18	8
Endocrine metabolic drugs	16	7
Gastrointestinal drugs	10	5
Oncology drugs	10	5
Diagnostic drugs	9	4
Blood modifier drugs	7	3
Musculoskeletal drugs	7	3
Ophthalmologic drugs	6	3
Respiratory drugs	6	3
Toxicology antidote drugs	6	3
Other ^a	18	8
Multiple therapeutic classes	8	4
Total	219	101^b

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

Notes: This figure reflects 219 of the 382 shortages (57 percent) reported during this time period. Our analysis was 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.

^aIncludes other therapeutic classes, such as dermatological drugs and immunological drugs, as well as 4 drugs whose therapeutic classes were unavailable from Red Book.

^bTotal does not sum to 100 due to rounding.

Providers Struggle to Respond to Drug Shortages without Adversely Affecting Patient Care

Provider association representatives told us that a number of the challenges that we reported in 2011 were still relevant for their members, including delays in or rationing of care, difficulties finding alternative drugs, risk associated with medication errors, higher costs, reduced time for patient care, and hoarding or stockpiling of drugs in shortage. During a shortage, providers may have to cancel or delay procedures, which can have detrimental health effects on patients.³⁴ Providers may also have to ration care by prioritizing the patients who have a greater need for the drug. For example, provider association representatives said that if a drug is used in patients across age groups, but is essential for the care of newborns, a hospital may institute a policy that the drug can only be administered to newborns and will no longer be administered to adults.

In addition, representatives from the provider associations noted that identifying effective, alternative drugs for those in shortage can be difficult. In some cases, it may not be possible to find a suitable alternative. For example, representatives from one of the associations we spoke to said that emergency service providers have reported significant difficulties finding alternative medications for stopping seizures and are concerned with the viability of alternative therapies in certain emergency situations. A representative from another association said that when effective alternatives are identified and located, medication errors may increase because the dosage of the alternative drug may differ from what providers are accustomed to using.

Drug shortages may result in higher drug costs as well as greater risks to patients. To obtain drugs in short supply, providers may turn to suppliers they do not typically use, including authorized alternative suppliers, compounding pharmacies, or gray market suppliers—those not authorized by the manufacturer to sell the drug—who typically obtain small quantities of a drug that is in short supply and offer it for purchase at an inflated price.³⁵ Drugs from alternative suppliers can cost

³⁴According to a 2011 American Hospital Association survey, over 80 percent of the 820 responding hospitals reported that patient treatment had been delayed as a result of drug shortages. See American Hospital Association, *AHA Survey on Drug Shortages* (Washington, D.C.: July 12, 2011).

³⁵Drug compounding is the process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a drug tailored to the medical needs of an individual patient. Compounding is typically used to prepare drugs that are not commercially available. See GAO, *Drug Compounding: Clear Authority and More Reliable Data Needed to Strengthen FDA Oversight*, [GAO-13-702](#) (Washington, D.C.: July 31, 2013).

significantly more, and, in the case of compounding pharmacies, and gray market suppliers, may pose risks to patients.³⁶ An outbreak of fungal meningitis in 2012 linked to contaminated compounded drugs—resulting in over 60 deaths and hundreds of people becoming ill—has led to questions about the safety and quality of compounded drugs.³⁷ Because the origin of a gray market drug may be unknown, there is no assurance that it was stored and transported appropriately. As a result, patients who receive treatment with such drugs may experience adverse events or receive inadequate or inappropriate treatment.³⁸ (See app. III for a description of steps federal agencies have taken to respond to gray market activities.)

Managing drug shortages also can detract from patient care. Providers may develop and institute policies for distributing drugs in short supply to patients, which some provider association representatives said may take time away from caring for patients. They may also need to become familiar with new products and different dosages, which may increase the risk for medication errors and take time away from patient care. Representatives from one provider association said that hospital

³⁶Higher costs resulting from drug shortages may also have implications for federal spending on drugs. Officials from federal agencies that are major purchasers of prescription drugs—including the Department of Defense, the Department of Veterans Affairs, the U.S. Coast Guard, the National Institutes of Health, and the Indian Health Service—generally told us that, as a result of drug shortages, there have been circumstances in which they paid more for drugs that were in short supply from suppliers from which they did not typically purchase. Though the alternative suppliers varied by agency, such purchases at a higher cost included those made directly from manufacturers, from authorized secondary wholesale distributors, and from other sources. (Officials from three of these agencies noted that purchases made directly from manufacturers and authorized secondary wholesale distributors were only slightly higher than the prices the agencies typically paid.) For the most part, officials from these agencies told us that they were not aware of any purchases from gray market suppliers and that the majority of their drug purchases are made through their typical, authorized purchasing channels. However, Indian Health Service officials told us that, on occasion, the agency has resorted to purchasing drugs from gray market suppliers to ensure patients and providers have access to needed drugs.

³⁷[GAO-13-702](#), 1.

³⁸The Institute for Safe Medication Practices reported in *Gray Market, Black Heart: Pharmaceutical Gray Market Finds a Disturbing Niche During the Drug Shortage Crisis* that over 10 percent of the 549 hospitals that participated in its July/August 2011 survey were aware of product authenticity issues, medication errors, or adverse drug reactions that were associated with the use of products purchased from the gray market. (Horsham, PA: Aug. 25, 2011).

pharmacists might need to devote more time than usual to work with the physician prescribing a drug that is in shortage to determine an appropriate therapeutic alternative.³⁹ In some instances, providers have hired full-time staff whose positions are entirely devoted to managing drug shortages. One provider association representative said a well-known hospital system has eight full-time employees who only work on addressing drug shortages. However, a few representatives noted that smaller providers may not have the resources to hire full-time employees and existing staff may have to take on additional responsibilities in order to respond to shortages.

Finally, the mere threat of a potential shortage can cause problems for patients and providers. While some provider association representatives reported that the lack of advance notice of a shortage hinders their ability to respond, most of the provider organizations we spoke with expressed concern that reports of an impending shortage can lead to the hoarding or stockpiling of drugs making it more difficult to access the drugs.⁴⁰

³⁹We previously reported that alternative drugs may be less effective, have a higher likelihood of adverse events, and may lead to medication errors, as health care providers may have to treat patients with drugs that are unfamiliar to them. See [GAO-12-116](#), 9.

⁴⁰To prevent potential hoarding and stockpiling during a shortage—as well as deter gray market operations—wholesale distributors may institute an allocation system, which provides any remaining inventory and any future shipments of the drug, by considering the customers' purchase history. For example, a wholesale distributor representative said that if a manufacturer is shipping only 50 percent of their prior volume of a given drug, a wholesale distributor's allocation system will only allow customers to purchase 50 percent of their historical purchase amount.

**Quality Problems
Coupled with
Constrained
Manufacturing
Capacity Are Often
the Immediate
Causes of Drug
Shortages, but There
Are Potential
Underlying Causes**

Quality problems resulting in supply disruptions coupled with constrained manufacturing capacity were frequently cited as the immediate causes of recent drug shortages. However, we also identified multiple potential underlying causes of shortages, all of which were related to the economics of the generic sterile injectable drug market.⁴¹

**Supply Disruptions
Stemming from Quality
Problems Frequently
Identified as Triggering
Recent Shortages**

**Quality Problems Leading to
Shortages**

The most frequently cited immediate cause for a drug shortage was that a manufacturer halted or slowed production after a quality problem was identified, resulting in a supply disruption. These supply disruptions were linked to, among other things, such problems as bacterial contamination or the presence of glass or metal particles in drug vials. Representatives from all eight manufacturers that we interviewed said that quality problems have contributed to recent shortages.⁴² Our analysis of FDA data shows that 40 percent of the shortages reported between January 1, 2011, and June 30, 2013, resulted from quality concerns, such as particulate matter or plant maintenance issues.⁴³ In addition, most of the

⁴¹In subsequent work, we intend to further explore the causes of drug shortages.

⁴²For the purposes of reporting, responses from “manufacturer representatives” include the responses from the five individual manufacturers and the three national manufacturer associations we interviewed.

⁴³The FDA data reflects information reported by manufacturers to FDA that is subsequently analyzed and categorized by the agency.

studies we reviewed (16 of 20) reported that concerns about product quality that led to supply disruptions have been the immediate cause of most shortages.⁴⁴ For example, one analysis found that quality problems were the cause linked to the majority of shortages of sterile injectable drugs.⁴⁵ Another study found that the immediate cause of 46 percent of all drug shortages in 2011 was a quality problem.⁴⁶ According to this study, the specific issues contributing to recent shortages have ranged from an inability to ensure the sterility of products to the identification of particulate matter in products.

According to another study, some of the largest manufacturers of sterile injectable drugs have had quality problems that they chose to address by temporarily closing or renovating their establishments, thereby reducing or temporarily ceasing manufacturing of multiple drugs and leading to supply disruptions.⁴⁷ Some of the temporary plant closures were proactively undertaken by the manufacturers themselves, while others were undertaken as part of their response to a warning letter from FDA.⁴⁸ Such plant closures to address quality problems with certain drugs or production lines can result in shortages of other drugs manufactured at these establishments, including those not associated with quality problems.⁴⁹ One study noted that many shortages that are classified as

⁴⁴For the purposes of reporting on our literature review—which included peer-reviewed articles, as well as government publications, and other journal articles that were not peer-reviewed—we identified and summarized the causes frequently discussed in the literature and did not list all topics mentioned in each article we reviewed. For example, we did not include causes that were mentioned only sparingly in the literature. Further, as shortages have been concentrated in the generic sterile injectable market in recent years, the literature on the subject of shortages and comments from manufacturer representatives largely focused on the causes of shortages specific to that market. As a result, our discussion about the causes of shortages may not be applicable to all shortages.

⁴⁵Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, *Economic Analysis of the Causes of Drug Shortages* (Washington, D.C.: October 2011), 13.

⁴⁶S.L. Kweder and S. Dill, “Drug Shortages: The Cycle of Quantity and Quality,” *Clinical Pharmacology & Therapeutics*, vol. 93, no. 3 (2013), 247.

⁴⁷Department of Health and Human Services, *Economic Analysis*, 13.

⁴⁸Reporting in March 2013, Kweder and Dill said that in the past 3 years, 4 of the top 10 manufacturers of sterile injectable drugs received warning letters from the FDA that they chose to address by closing establishments or slowing production. See Kweder and Dill, “Drug Shortages,” 248.

⁴⁹Kweder and Dill, “Drug Shortages,” 247.

being caused by delays and capacity issues are technically caused by supply disruptions related to quality.⁵⁰ Our analysis of FDA data indicates that manufacturing delays or capacity issues accounted for 30 percent of the shortages reported between January 1, 2011, and June 30, 2013. FDA officials told us that delays or capacity issues that triggered shortages typically involved temporary shutdowns or slowdowns undertaken to perform maintenance or, in many recent cases, for remediation efforts, which then caused supply disruptions.⁵¹

Although quality problems were a frequently cited issue, there was not complete agreement as to whether quality problems were truly the trigger for the supply disruptions that cause shortages. Specifically, one study concluded that FDA has applied CGMPs more rigorously in its inspections of manufacturing establishments, resulting in a greater number of quality problems being identified and thus leading to manufacturing supply disruptions that then triggered shortages.⁵² Another study suggested that an increase in FDA inspections of injectable drug manufacturing establishments without evidence of an increase in quality problems has contributed to shortages of generic sterile injectable

⁵⁰J. Woodcock and M. Wosinska, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages," *Clinical Pharmacology & Therapeutics*, vol. 93, no.2 (2013), 171.

⁵¹In this way, quality problems can ultimately trigger supply disruptions for drugs for which a quality problem has not been identified. For example, if a specific product or production line in a manufacturing establishment is found to have a quality problem, a manufacturer may shut down the entire establishment or change its manufacturing schedule at that establishment while trying to correct the quality problem. This shutdown or change may affect the manufacturing of other drugs produced at the establishment and lead to shortages of those drugs, even if no quality problems have been identified with those other drugs. FDA would classify the cause of the shortage of the original drug as a quality problem, but it would classify the cause of any shortages of the other affected drugs as a manufacturing delay and capacity issue.

⁵²U.S. House of Representatives, Committee on Oversight and Government Reform, Staff Report, "FDA's Contribution to the Drug Shortage Crisis," (Washington, D.C.: June 2012), 16-18. As evidence of increased rigor in FDA inspections, this study cites, in part, an overall increase in the number of warning letters issued. FDA officials told us that the increase in the number of warning letters issued by the agency between 2010 and 2011 that was cited in the study was primarily due to the activities of the agency's Center for Tobacco Products. FDA officials also stated that during this time the level of warning letters issued to firms for manufacturing quality deficiencies decreased.

drugs.⁵³ In addition, one manufacturer representative noted that FDA investigators throughout the country may differ in their interpretations of CGMPs, which the representative said creates uncertainty about whether a manufacturer's current processes will be found to be in compliance during an FDA inspection. Therefore, from this manufacturer's perspective, FDA's compliance actions have been the primary cause of shortages with quality problems being a secondary cause. A second manufacturer representative said that though quality problems have contributed to recent shortages, from the manufacturer's perspective, quality standards have also been raised. However, one study countered the claim that FDA's enforcement has changed by stating that manufacturers often identify quality problems and it is their discoveries that trigger FDA inspections in the first place, rather than an increase in agency scrutiny. This study also noted that CGMPs, which provide a framework for a manufacturer to produce safe, pure, and high-quality drugs, have not changed in recent years.⁵⁴ One manufacturer representative concurred that the CGMPs themselves had not changed. However, this representative noted that as manufacturing technology advances, the expectations of FDA investigators as to what represents quality manufacturing may advance as well. For example, as new manufacturing equipment becomes available, FDA investigators may expect manufacturers to install the new equipment, even if using older equipment will result in drugs of the same quality.⁵⁵

Other Immediate Causes of Shortages

Although not as prominently cited in the literature or the FDA data as quality problems, we identified a number of additional factors that can cause supply disruptions and ultimately result in shortages.

⁵³ John R. Graham, *The Shortage of Generic Sterile Injectable Drug: Diagnosis and Solutions* (Midland, Mich.: Mackinac Center for Public Policy, June 2012), 5. FDA officials told us that inspections of sterile injectable manufacturing establishments have long been a high priority and such sites receive regular inspections.

⁵⁴ Kweder and Dill, "Drug Shortages," 248.

⁵⁵ According to FDA officials, the agency does not require manufacturers to adopt state of the art technology or use the most modern manufacturing equipment in drug production or testing to meet its standards of quality. FDA officials also said requirements and inspections do not, as a rule, specify or limit the type of equipment or technology used in drug manufacturing, although FDA encourages the voluntary adoption of new technology that leads to improved drug quality.

Permanent product discontinuations: Permanent product discontinuations were another immediate cause of shortages. Our analysis of FDA data shows that 12 percent of the shortages reported between January 1, 2011, and June 30, 2013, resulted from product discontinuations. According to several studies, the generic drug market is extremely concentrated, with few manufacturers producing each drug. For example, one study found that most generic sterile injectable drugs are made by three or fewer manufacturers.⁵⁶ As a result, the discontinuation of a drug by a single manufacturer can have a significant impact on drug availability. Two studies noted that older generic drugs may be discontinued in favor of producing newer drugs that are more profitable or that have more demand.⁵⁷ Three manufacturer representatives said that they take a number of factors into account when determining whether to discontinue manufacturing a drug. The first manufacturer representative said that in addition to price, they will also account for factors such as the medical necessity and importance of the drug when making decisions about what drugs to manufacture. The second manufacturer representative said that they do not discontinue products if they know that doing so would cause a shortage or exacerbate an existing one, although the same representative also said that products with low sales or profitability may be de-emphasized in favor of producing drugs with greater demand. The third manufacturer representative also noted that it is likely that a lower-margin product would be discontinued rather than a higher-margin product. Two manufacturer representatives said that if a drug is already in shortage, they will try to continue to manufacture it, even at low or negative profit margins, to ensure that the drug remains in the market.

Unavailability of raw materials or components: The unavailability of raw materials, such as an active pharmaceutical ingredient (API), and non-API components, such as vials, also contributes to shortages.⁵⁸ The

⁵⁶Department of Health and Human Services, *Economic Analysis*, 6.

⁵⁷V. Jensen, R. Kimzey, and J. Saliba, "An Overview of the FDA's Drug Shortage Program," *Pharmacy and Therapeutics*, vol. 30, no. 3 (2005); and V. Jensen and B. A. Rappaport, "The Reality of Drug Shortages—The Case of the Injectable Agent Propofol," *The New England Journal of Medicine*, vol. 363, no. 9 (2010).

⁵⁸An API is any element that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. Non-API components include inactive ingredients, such as dyes or water for injection, and items such as vials and stoppers. See 21 C.F.R. § 210.3(b)(3), (7) (2013).

majority of the studies we reviewed cited the unavailability of raw materials or non-API components as a cause of shortages and two reported that there is often only one API source for a given drug.⁵⁹ This dependency on a sole API source can lead to shortages if availability becomes a problem, regardless of the number of manufacturers of a particular product.⁶⁰ Most of the manufacturers' representatives agreed that the unavailability of API has caused some shortages, although some representatives said that it was a relatively small percentage of them. For example, a representative from one manufacturer said that the 2011 tsunami in Japan disrupted the API supply for one of its products and led to a shortage. Although the manufacturer ultimately identified another source for the needed material, FDA had to approve the manufacturer's new source, which was time-consuming. In addition, two manufacturer representatives mentioned that issues with non-API components had contributed to shortages. Our analysis of FDA data shows that 9 percent of the shortages reported between January 1, 2011, and June 30, 2013, resulted from the unavailability of APIs or non-API components.

Loss of a manufacturing site or site change: Our analysis of FDA data shows that 3 percent of the shortages reported between January 1, 2011, and June 30, 2013, were due to either the loss of a manufacturing site or site change. One manufacturer representative said that while manufacturers have experienced disruptions due to natural disasters, this has been rare. In the literature, half of the studies (10 of 20) mentioned natural disasters, such as floods or hurricanes, as a cause of shortages. Loss of, or damage to, a manufacturing site was typically given as an example of the supply disruption resulting from the disaster.

Increased demand: In addition to events that result in changes in supply, we found that shortages can also be triggered by changes in demand. Our analysis of FDA data shows that 6 percent of the shortages reported between January 1, 2011, and June 30, 2013, were due to increased demand. An increase in demand, which may occur for a variety of reasons, such as the approval of an already marketed drug for a new indication or new therapeutic guidelines, can trigger a shortage. A

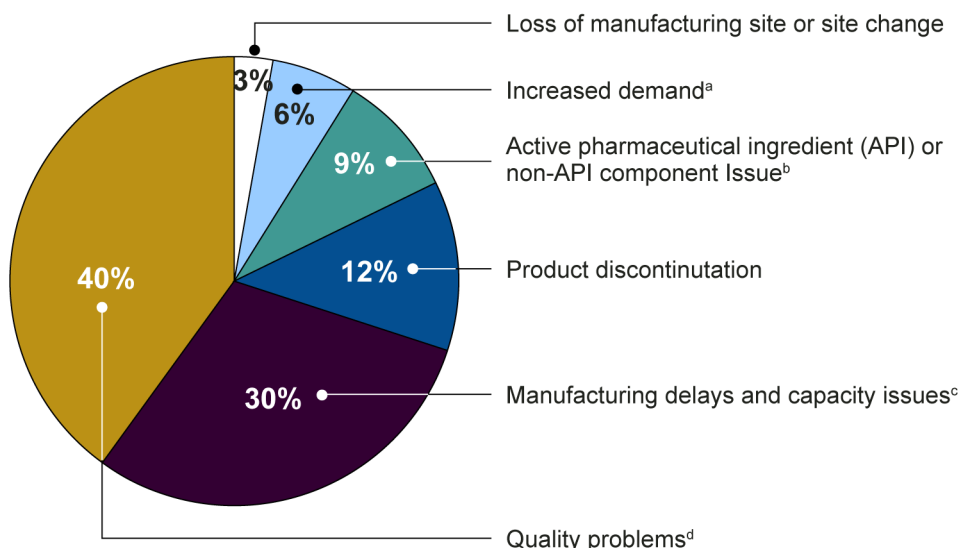
⁵⁹B.K. Gehrett, "A Prescription for Drug Shortages," *JAMA: The Journal of the American Medical Association*, vol. 307, no. 2 (2012); and Jensen, Kimzey, and Saliba, "An Overview," 175.

⁶⁰Jensen, Kimzey, and Saliba, "An Overview," 175.

shortage results because manufacturers cannot keep up with the increase in demand that exceeds their expectations or planned production. Increased demand was cited as a cause of shortages in 9 of the 20 studies we reviewed.

Figure 6 summarizes information reported by manufacturers to FDA about the causes of drug shortages that the agency then analyzes and categorizes.

Figure 6: Reported Causes of Drug Shortages from January 2011 through June 2013



Source: GAO analysis of FDA data.

Notes: This figure summarizes our analysis of information reported by manufacturers to FDA about the causes of drug shortages that the agency then analyzes and categorizes.

^aFDA defines increased demand as an increase in the request for a product relative to its traditional usage. For example, if FDA approves the drug for a new indication, demand may increase.

^bAn API is any element that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. Non-API components include inactive ingredients such as dyes or water for injection, and items such as vials and stoppers. See 21 C.F.R. § 210.3(b)(3), (7) (2013).

^cManufacturing delays and capacity issues normally involve shutdowns or slowdowns of facilities or production lines in order to perform maintenance or for remediation efforts. For example, a shutdown of a production line to address a quality problem with one drug may delay manufacturing of all other drugs on that line, even if no quality problems have been identified with those other drugs.

^d“Quality problems” includes the identification of such issues as bacterial contamination or particulate matter (i.e., metal or glass particles in vials).

Constrained Manufacturing Capacity Often Viewed as Limiting Manufacturers' Ability to Respond to Supply Disruptions

The inability of other manufacturers to make up for supply disruptions experienced by their competitors due to constrained manufacturing capacity was another immediate cause of shortages. Several of the studies we reviewed generally concluded that the heavy concentration of the generic drug industry leaves few manufacturers available to respond to supply disruptions, leading to market-wide shortages.⁶¹ One study found that seven manufacturers dominate the generic sterile injectable market overall and also found that this market is even further concentrated for specific therapeutic classes.⁶² Specifically, this analysis indicated that in 2008, three manufacturers produced 71 percent of all generic sterile injectable oncology drugs and that three manufacturers held 91 percent of the market share of generic sterile injectable nutrients and supplements. Illustrating the interplay between supply disruptions and constrained manufacturing capacity, one 2010 study reported that a shortage of the generic sterile injectable anesthesia drug propofol resulted after one of the three manufacturers of the drug permanently discontinued its manufacturing and another experienced quality problems leading to a temporary halt in production, leaving the remaining manufacturer unable to meet the demand of the entire market.⁶³

In addition to consisting of few manufacturers overall, we also found that the manufacturing capacity of the generic drug industry has been further challenged in recent years as the industry has expanded the number of generic products it manufactures. This expansion has resulted as a large number of brand-name drugs have lost patent protection, clearing the way for generic manufacturers to produce generic equivalents of these drugs. Two of the studies we examined cited the decisions of manufacturers to begin producing the generic equivalents of brand-name drugs as contributing to shortages by stretching already limited capacity. For example, one study found that the generic sterile injectable market had expanded by 52 percent between 2006 and 2010 without a commensurate increase in manufacturing capacity, leading to high

⁶¹We also reported on this challenge in 2011, as both officials from FDA and manufacturers told us that when only a few manufacturers make a drug and one manufacturer's drug is in short supply, it can be difficult for the others to substantially increase production of a drug to ensure that demand for a drug is met. See [GAO-12-116](#), 26.

⁶²Woodcock and Wosinska, "Economic and Technological Drivers," 174.

⁶³Jensen and Rappaport, "Reality of Drug Shortages," 806.

utilization of available manufacturing capacity.⁶⁴ Representatives from two manufacturers said that faced with limited capacity, when new generics are available for production a manufacturer may make the decision to stop producing some drugs to make room for the new products. As a result, such discontinuations could lead to shortages, but representatives from both manufacturers characterized this as a small factor in causing shortages.

In addition to the challenge presented by having few manufacturers and the increase in the number of generic drugs, pressures to produce this large number of drugs on only a few manufacturing lines leaves the manufacturers that do participate in the generic sterile injectable market with little flexibility.⁶⁵ Since multiple drugs are often manufactured on the same line, increasing production of one drug reduces the supply of other drugs and can lead to shortages.⁶⁶ For example, one manufacturer representative said that there are usually anywhere from 30 to 50 different drugs manufactured on a given line. Further, according to one study, manufacturers of generic sterile injectable drugs do not typically have redundant manufacturing facilities.⁶⁷ Specifically, in a review of almost 900 generic sterile injectable applications that were submitted to the FDA and approved between 2000 and 2011, the authors found that only 11 applications (about 1 percent) referenced a backup facility. This becomes problematic when production in a given facility must stop for any reason as manufacturers cannot immediately move production of a drug to another facility. To do so, they must first obtain approval from FDA, which can further delay production.

A related constraint cited in the literature is that some generic sterile injectable drugs need to be manufactured on lines or in facilities dedicated solely to those drugs. One study noted that certain sterile injectable products, such as anti-infective and oncology drugs, require lines, and sometimes whole facilities, which are limited to the production

⁶⁴Department of Health and Human Services, *Economic Analysis*, 9.

⁶⁵Department of Health and Human Services, *Economic Analysis*, 6; and Jensen and Rappaport, "Reality of Drug Shortages," 806.

⁶⁶C. L. Ventola, "The Drug Shortage Crisis in the United States: Causes, Impact, and Management Strategies," *Pharmacy and Therapeutics*, vol. 36, no.11 (2011).

⁶⁷Woodcock and Wosinska, "Economic and Technological Drivers," 174.

of such drugs.⁶⁸ For example, some anti-infective drugs, such as penicillin, are highly sensitizing and can trigger serious allergic reactions at very low levels and as a result, may be limited to specific manufacturing lines. Further, another study noted that a supply disruption on a dedicated line can result in shortages of multiple products of a similar type, such as oncology drugs, because other manufacturers are not able to step in due to limited capacity on their own lines.⁶⁹ For example, shortages of oncology drugs in 2011 were linked to just three dedicated oncology lines that were operated by two manufacturers.

A final capacity-related constraint cited in the literature (9 of 20 studies), was how the widespread use of “just-in-time” inventory practices can increase the vulnerability of the supply chain to shortages.⁷⁰ One of these studies said that most manufacturers only produce enough of a drug to satisfy current demand, so there is little, if any excess inventory, while another study asserts that when a manufacturer has to stop production, a supply disruption can result because of “just-in-time” inventory.⁷¹ One manufacturer representative said that any manufacturer typically has only a limited amount of inventory available. This representative said that manufacturers typically have about 2 to 3 months of inventory on hand, wholesale distributors usually have about 1 month, and providers only have a few weeks of inventory. Consequently, if an issue arises, a shortage can quickly result.

The majority of manufacturer representatives we interviewed generally concurred with our finding from the literature that a supply disruption, for whatever reason, affecting one manufacturer can quickly lead to market-wide shortages because other manufacturers often cannot increase production enough to meet demand. For example, one manufacturer representative said that it had recently encountered capacity constraints

⁶⁸Woodcock and Wosinska, “Economic and Technological Drivers,” 174.

⁶⁹Department of Health and Human Services, Food and Drug Administration, *A Review of FDA’s Approach to Medical Product Shortages*. (Silver Spring, Md: October 2011).

⁷⁰For example, see American Society of Health-System Pharmacists, “ASHP Guidelines on Managing Drug Product Shortages in Hospitals and Health Systems,” *American Journal of Health-System Pharmacy*, vol. 66, no.15 (2009); and Ventola, “Drug Shortage Crisis in the United States,” 749.

⁷¹Jensen and Rappaport, “Reality of Drug Shortages,” 806, and Gehrett, “Prescription for Drug Shortages,” 154.

when two other manufacturers experienced supply disruptions and one manufacturer exited the market. The representative from the manufacturer that remained said that the company did not have the capacity to ramp up production to meet the demand for all of the drugs at risk of shortage and thus had to prioritize which drugs to produce, based on market need and the severity of the shortages. Further complicating a situation like this, representatives of two manufacturers said that even if the remaining companies are able to increase their production of a drug whose supply has been disrupted, it can take time—as much as 3 months—to increase production, particularly for sterile injectables due to the complexity of manufacturing these products.

Drug Shortages May Stem From Underlying Causes

We identified multiple potential underlying causes of drug shortages in the literature. Half of the studies (10 of 20) we reviewed suggested that the immediate causes of drug shortages, such as quality problems, are driven by an underlying cause that stems from the economics of the generic sterile injectable drug market. The studies that cited underlying causes did not all focus on the same underlying cause and manufacturer representatives had mixed views on the potential underlying causes we identified in the literature.⁷²

Competition Focused Primarily on Price

One underlying factor we identified in the literature is that when choosing between different manufacturers of the same drug, purchasers may focus primarily on price. Six of the 20 studies mentioned either low prices or low profit margins as features of the generic drug market that may make it vulnerable to shortages. Two of the studies suggested that low profit margins in the generic market may affect manufacturers' decisions to invest in their facilities.⁷³ Another of the six studies said that purchasers expect all generic drugs to be of equivalent quality and may be unable to

⁷²Most manufacturer representatives (5 of 8) did not provide comments on all underlying causes discussed, but all provided comments on at least one.

⁷³Gehrett, "Prescription for Drug Shortages," 154; and S. O. Schweitzer, "How the U.S. Food and Drug Administration Can Solve the Prescription Drug Shortage Problem," *American Journal of Public Health*, vol. 103, no. 5 (2013): e10-e14.

discern differences in the quality of drugs, particularly sterile injectables.⁷⁴ As a consequence, purchasers of sterile injectables focus on price when choosing among seemingly identical generic manufacturers at the expense of any potential differences in quality and the ability to reliably meet customer demand. According to this study, a manufacturer that strives to exceed minimum manufacturing standards is not rewarded with a willingness among buyers to pay more for the manufacturer's products. Therefore, using economic theory as a rationale, the authors suggested that this reduces the incentive for the manufacturer to sufficiently invest in maintenance or quality improvements at its manufacturing establishments. The study suggests that the lack of reward for quality is an underlying cause that may have led to manufacturers' minimizing investment in establishments, which has ultimately resulted in many of the recent quality problems at generic sterile injectable manufacturing establishments.⁷⁵

Five of the six drug manufacturer representatives that responded to this claim reported that manufacturers continue to invest in upgrading existing establishments and building new ones.⁷⁶ One manufacturer representative stated that some generic products in manufacturers' portfolios are highly profitable and prompt investments in manufacturing facilities. Another manufacturer representative said that they continue to invest in making improvements to their sterile injectable facilities. For example, they said that they have invested in spare capacity on some of their lines, and as a result, are now better equipped to ramp up production in response to a shortage.

⁷⁴Woodcock and Wosinska, "Economic and Technological Drivers," 170. The authors point out that purchasers may be unable to discern differences in the quality of sterile injectables because the patients that receive them often have compromised immune systems and other health complications. Consequently, any adverse health outcomes, such as infection following the treatment, are likely attributed to patients' health status rather than possible quality problems associated with the drugs.

⁷⁵According to this study, the quality of brand-name products may be equally difficult to observe. However, the authors argue, brand-name manufacturers' incentive to minimize investments in quality is counteracted by the incentive to avoid losing revenue on high-margin products due to an interruption in production. See Woodcock and Wosinska, "Economic and Technological Drivers," 175.

⁷⁶Not all of the manufacturer representatives we interviewed provided comments on this claim. Specifically, two of the eight manufacturers did not provide comments.

Role of Group Purchasing Organizations

Group purchasing organizations (GPO), which negotiate purchasing contracts with drug manufacturers on behalf of hospitals and other health care providers, have been cited in the literature as potentially having an underlying role in causing drug shortages.⁷⁷ Four of the 20 studies suggested that the operating structure of GPOs results in fewer manufacturers producing generic drugs and this, in turn, contributes to a more fragile supply chain for these drugs.⁷⁸ For example, one of the four studies asserted that GPOs reduce profits in the generic drug market, where margins are already low.⁷⁹ This study states that because of these low manufacturer profit margins, when production problems arise, manufacturers may stop producing certain products in lieu of making investments in improvements at their establishments.⁸⁰ Another of the four studies theorized that when generic drug manufacturers fail to win GPO contracts, manufacturers will either exit or decide not to enter the market for those drugs, contributing to the immediate cause of constrained manufacturing capacity.⁸¹

All of the representatives of the three GPOs that we contacted disagreed with the claim that GPOs are a cause of shortages. They emphasized that they have an incentive to avoid drug shortages and ensure that the drug manufacturers with which GPOs contact can meet GPOs' members' needs. Further, they said that while price is an important consideration in

⁷⁷Through GPO-negotiated contracts, hospitals and other health care providers can purchase a variety of medical products, including drugs. According to a GPO association, pooling the purchasing power of multiple providers allows GPOs to negotiate lower prices on products from vendors. Sterile injectable drugs—where shortages have recently been concentrated—are primarily purchased by hospitals and physicians' offices rather than directly by consumers. In addition, most of these drugs are purchased through GPO-negotiated contracts. See Department of Health and Human Services, *Economic Analysis*, 5.

⁷⁸See Kweder and Dill, "Drug Shortages," 249; Schweitzer, "How the U.S. Food and Drug Administration," *American Journal of Public Health*, e11; Department of Health and Human Services, Food and Drug Administration, "Review of FDA's Approach," 26,30; and U.S. House of Representatives, "FDA's Contribution," 9-10.

⁷⁹Kweder and Dill, "Drug Shortages," 249.

⁸⁰In addition to the four articles in our literature review that cited a role for GPOs in causing shortages by contributing to low manufacturer profit margins through downward price pressure, other commentators have suggested that administrative and other fees that manufacturers typically pay GPOs have contributed to shortages by further reducing the profit margins associated with these drugs.

⁸¹U.S. House of Representatives, "FDA's Contribution," 10, 20.

determining the manufacturers with whom they contract, the ability of manufacturers to ensure an adequate supply of products is critical. According to one GPO representative, generic drug manufacturers are generally profitable, which the GPO representative said demonstrates that manufacturers are not being driven out of the market. All of the GPO representatives also noted that in recent years GPOs have instituted strategies to avoid shortages. For example, one GPO representative told us that it typically tries to contract with two or more manufacturers for drugs that have a recent history of being in shortage.

Of the five manufacturer representatives who commented on the claim, three stated that GPOs may contribute to shortages by exerting downward price pressure.⁸² However, one manufacturer representative disagreed that GPOs were a cause and a second manufacturer representative said that GPOs had no more of a role in causing shortages than any other supply chain participant. While the second representative said that GPOs contribute to the pressure to lower prices, the representative also noted that every participant in the supply chain contributes to the price competition. A third manufacturer representative noted that, because manufacturers have already made investments in production that they are unwilling to abandon, failing to obtain a GPO contract does not cause them to exit the market for a given drug. Further, representatives from the second and third manufacturers also told us that, in the event that a major manufacturer does not obtain a GPO contract, the manufacturer may send its sales force to hospitals directly and offer a price that is lower than the GPO contract price. Hospitals may either accept this lower priced offer or seek additional price concessions from the contracted manufacturer through the GPO.

Change in Medicare Part B Reimbursement Policy

A change in Medicare Part B drug reimbursement policy was also cited in the literature (5 of 20 studies) as an underlying cause of drug shortages. In 2005, a change was implemented in how providers are reimbursed for

⁸²Not all of the manufacturer representatives we interviewed provided comments on this claim. Specifically, three of the eight manufacturers did not provide comments about GPOs and drug shortages.

most Medicare Part B drugs administered in an outpatient setting.⁸³ Three studies we reviewed suggested that this change resulted in a sharp decrease in reimbursement to providers.⁸⁴ One of the studies, which focused on oncology drugs, suggested that this decrease in reimbursement caused providers to switch to higher-cost drugs for which they would receive increased reimbursement, reducing demand for

⁸³Medicare Part B covers a limited number of prescription drugs, generally covering drugs and biologicals administered under a physician's direct supervision, including many injectable drugs administered in physician offices and in hospital outpatient departments. Part B also covers certain drugs administered through durable medical equipment, certain vaccines, osteoporosis drugs, erythropoiesis-stimulating agents, certain oral anti-cancer drugs, and immunosuppressive drugs for transplant patients. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 modified the reimbursement methodology for Part B drugs. Pub. L. No. 108-173, § 303(c), 117 Stat. 2066, 2239 (2003). Beginning January 1, 2005, the Medicare reimbursement methodology for most Part B drugs that are not administered on a cost or prospective basis was changed to 106 percent of the drug's volume-weighted average sales price. Average sales price is the weighted average of all non-federal U.S. sales by manufacturers net of chargebacks, discounts, rebates, and other price concessions made by the manufacturer and tied to the purchase of the drug product, whether it is paid to the wholesale distributor or the entity that purchases the drug. Prior to the change, Medicare reimbursed for 95 percent of the average wholesale price, which studies indicate for many drugs was significantly higher than the prices actually paid by physicians and suppliers who purchase the drugs. Certain Part B drugs continue to be paid at 95 percent of the average wholesale price. These include blood products, and certain vaccines. Infusion drugs used in conjunction with durable medical equipment are also paid at 95 percent of the average wholesale price in effect on October 1, 2003.

⁸⁴A. Yurukoglu, "Medicare Reimbursements and Shortages of Sterile Injectable Pharmaceuticals," National Bureau of Economic Research Working Paper No. 17987 (2012); M. L. Gatesman and T.J. Smith, "The Shortage of Essential Chemotherapy Drugs in the United States," *The New England Journal of Medicine*, vol. 365, no. 18 (2011); and U.S. House of Representatives, "FDA's Contribution," 4.

generics.⁸⁵ The other two studies suggested that this decrease in reimbursement to providers also resulted in lower prices for manufacturers.⁸⁶ Two of the three studies suggested that manufacturers responded by exiting the market for these products entirely, while the third suggested that manufacturers reduced their investments in manufacturing facilities, both of which left the generic sterile injectable market vulnerable to shortages.⁸⁷

Four of the five manufacturer representatives who responded to this claim did not view the change in Part B reimbursement policy as a main cause of shortages, though they said it could have complicated the generic

⁸⁵Because Part B drug reimbursement equals the average sales price plus a fixed percentage (6 percent for most drugs), some suggest that providers have an incentive to prescribe relatively higher-cost drugs, when they are available, as higher-cost drugs provide a larger markup. For example, if the average sales price for a given drug is \$150, the Part B reimbursement would provide an additional \$9 on top of the \$150. If an alternative drug is available with the average sales price of \$3,000, the Part B reimbursement would provide an additional \$180 on top of the \$3000. (A given provider's actual purchase price may be more or less than the average sales price on which the Centers for Medicare & Medicaid Services bases the reimbursement.) While not a study about drug shortages, another study found that as a result of the Medicare Part B reimbursement change, physicians who were providing chemotherapy treatment to Medicare beneficiaries newly diagnosed with lung cancer switched to higher cost drugs and away from drugs that experienced large drops in payment rates after the reimbursement change. See M. Jacobsen, C.C. Earle, M. Price, and J.P. Newhouse, "How Medicare's Payment Cuts For Cancer Chemotherapy Drugs Changed Patterns of Treatment," *Health Affairs*, vol. 29, no. 7 (2010).

⁸⁶Another study we reviewed analyzed prices and volume in the sterile injectable oncology market from 2006 through 2011. This study found that, on average, drugs that subsequently experienced a shortage were those in which the volume of sales and prices were both declining in the period prior to the recent increase in shortages. However, this study did not directly attribute the declines in sales volume and prices to the reimbursement change. See Department of Health and Human Services, *Economic Analysis*, 7-8.

⁸⁷Another analysis reported that the trend in shortages has been similar both for drugs affected by the reimbursement change and for drugs that should not have been affected. See M. Jacobsen, A. Alpert, and F. Duarte, "Prescription Drug Shortages: Reconsidering the Role of Medicare Payment Policies," in *Health Affairs Blog*, (May 29, 2012), accessed November 26, 2013, <http://healthaffairs.org/blog/2012/05/29/prescription-drug-shortages-reconsidering-the-role-of-medicare-payment-policies/>.

market.⁸⁸ For example, one manufacturer representative contended that it had a negligible impact at most as the reimbursement is paid to physicians, not manufacturers. The payments that manufacturers collect are several steps removed from the physician's reimbursement. In addition, the representative stated that even if some providers switch to more expensive alternative drugs in response to the reimbursement change, the impact would be minimal as the vast majority of generic sterile injectables are administered in hospital inpatient departments, which means that they are not reimbursed through Medicare Part B.⁸⁹ Finally, though drugs in at least one of the therapeutic classes that have most frequently been in shortage in recent years may be reimbursed through Part B based on the Average Sales Price methodology, the

⁸⁸Representatives of one of the five manufacturers that responded agreed with the claim that the Part B reimbursement change was a cause of shortages. However, they did not provide any additional rationale to explain their statement. In total, we asked eight manufacturer representatives about this claim. However, three of them did not offer their view as to whether or not the change in Part B reimbursement was a cause of shortages.

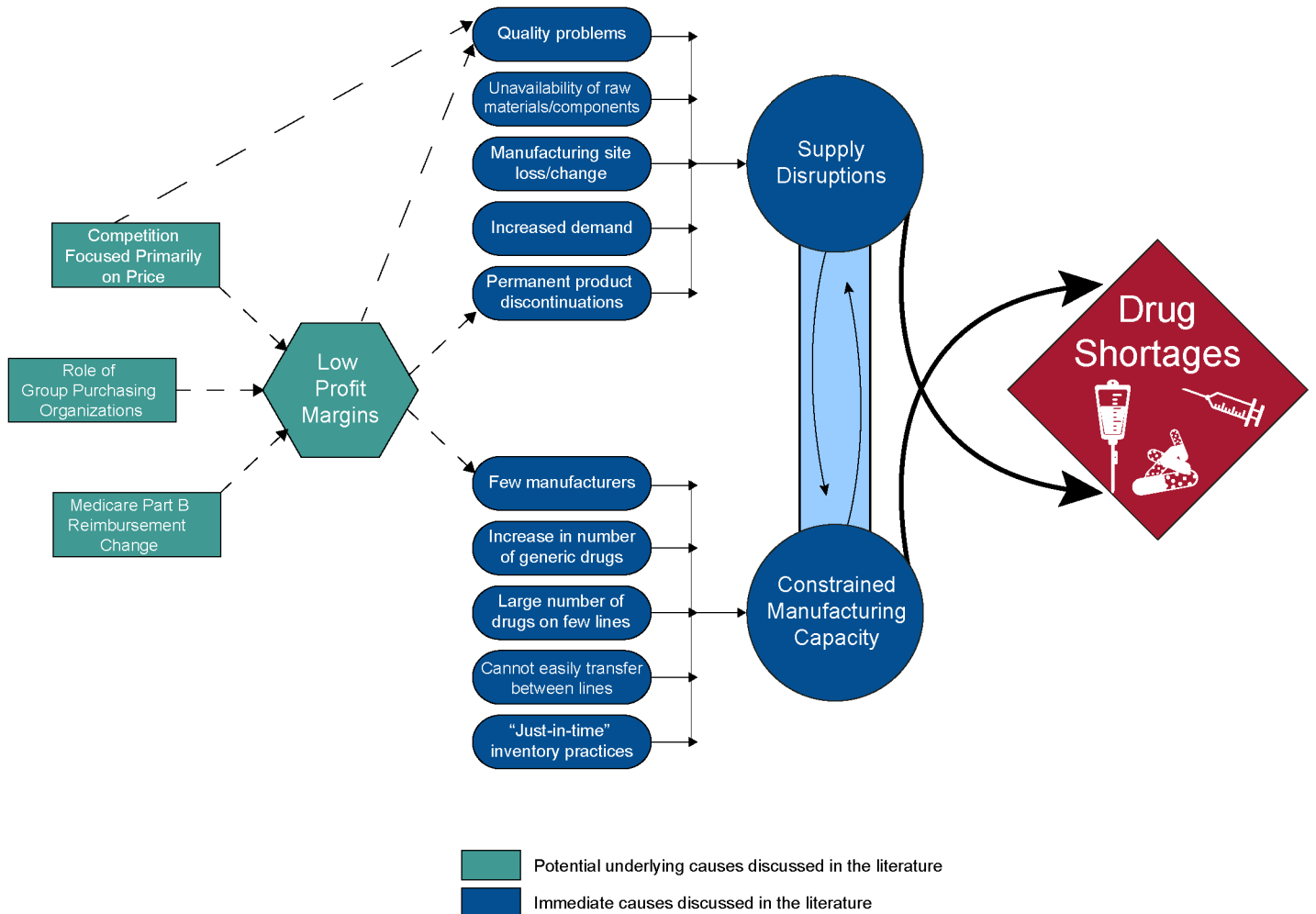
⁸⁹This point was also noted in one of the studies that cited the reimbursement change as a cause, stating that although the reimbursement change increased concentration in the generic injectable market and reduced manufacturer incentives to invest in their facilities, most injectables that have been in shortage are typically administered in hospitals, and thus, would not be impacted a great deal by the change in Part B reimbursement. See U.S. House of Representatives, "FDA's Contribution," 14.

extent to which all of the therapeutic classes driving recent shortages are reimbursed in this manner is unclear.⁹⁰

Figure 7 summarizes the key immediate and potential underlying causes of drug shortages that we found in our review of the literature.

⁹⁰In order to set the reimbursement rate for Medicare Part B drugs, the Centers for Medicare & Medicaid Services collects average sales price data from manufacturers. Manufacturers submit sales data at the national drug code (NDC) level, which uniquely identifies a specific drug product for a given manufacturer. (One drug can have multiple NDCs associated with it. For example, a drug made by one manufacturer, in one strength, but in three package sizes, would have a different NDC for each of the three package sizes.) CMS sets reimbursement rates at the Healthcare Common Procedure Coding System (HCPCS) level, with multiple NDCs associated with a given HCPCS code. In reporting Medicare Part B reimbursement rates, the Centers for Medicare & Medicaid Services provides an NDC/HCPCS crosswalk. We reviewed whether NDCs for 12 drugs in the therapeutic classes of oncology, nutritive, and anesthesia and central nervous system, all of which were among the classes most frequently in shortage in recent years, were contained in the most recent NDC/HCPCS crosswalk, which at the time of our analysis was the October 2013 crosswalk. Specifically, we asked representatives of relevant health care professional associations for suggestions of the most significant recent shortages in each of these therapeutic classes and randomly selected four drugs in each therapeutic class from these suggestions. We then compared the NDCs associated with these shortages to the most recent NDC/HCPCS crosswalk posted on the Centers for Medicare & Medicaid Services' website. We found that the NDC/HCPCS crosswalk included: all NDCs for three of four oncology drugs (cytarabine, doxorubicin, and methotrexate) and nearly all NDCs for the fourth (paclitaxel); all NDCs for one of four nutritive drugs (calcium gluconate); and half of the NDCs for one of four anesthesia and central nervous system drugs (epinephrine). (For the oncology drug that had nearly all NDCs in the crosswalk, 3 of 22 NDCs were not found in the crosswalk. All of the missing NDCs were associated with the same manufacturer. For the anesthesia and central nervous system drug that had some NDCs in the crosswalk, 6 of 12 NDCs were not in the crosswalk.) However, the crosswalk did not include these data for three of the four nutritive drugs (calcium chloride, intravenous fat emulsion, and sodium phosphate) or three of the four anesthesia and central nervous system drugs (neostigmine, propofol, and succinylcholine). This suggests that nutritive drugs and anesthesia and central nervous system drugs may not all be reimbursed using the average sales price plus 6 percent methodology.

Figure 7: Key Immediate and Potential Underlying Causes of Drug Shortages Discussed in Literature



Source: GAO analysis based on review of literature.

FDA Is Improving Its Response to Drug Shortages, but Challenges Remain

Through a variety of efforts, FDA has prevented more potential shortages and improved its ability to respond to shortages since we issued our report in 2011. Among other things, FDA is working to improve its response to drug shortages by implementing FDASIA's requirements and the recommendations we made in 2011. However, FDA lacks policies and procedures for managing and using information from its drug shortage database.

FDA Has Prevented More Potential Shortages and Has Improved Its Ability to Respond to Shortages That Do Occur

FDA has taken steps that have prevented more potential shortages and improved its ability to resolve existing drug shortages since 2011, including expediting review of ANDAs and supplements, working with manufacturers to increase production, and using its regulatory discretion to allow certain products to remain on the market or bring new products to market.⁹¹ Based on our analysis of FDA data from January 2011 through June 2013, FDA was able to prevent 89 potential shortages in 2011, 154 potential shortages in 2012, and 50 potential shortages through June 2013.⁹² This is more than the 35 potential shortages we found that FDA prevented in 2010 and the 50 prevented through June 2011. FDA officials told us that although they relied on many of the same steps to prevent and resolve shortages prior to the enactment of FDASIA, FDASIA's requirement that manufacturers notify FDA in advance of a potential shortage allowed FDA to employ those steps sooner.⁹³ FDA officials said the notification requirement has helped the agency become more

⁹¹For information on incentives that have been proposed to prevent shortages, see app. IV.

⁹²As we did in analyzing data for our 2011 report, we grouped together shortages of multiple versions of the same drug to identify the total number of potential shortages prevented. While FDA had reported preventing 195 potential shortages in 2011, 282 potential shortages in 2012, and 80 potential shortages through June 2013, we found that these data represented the number of individual drug products for which a shortage had been averted. FDA officials said they count different package sizes and concentrations of a given drug as separate prevented potential shortages because additional effort may be required by FDA to prevent the potential shortage of individual versions of the drug. For example, FDA would count the prevention of a potential shortage of a 250 ml package size and the 500 ml package size of the same drug as two potential shortages prevented. FDA officials said they count a potential shortage as prevented if they are made aware of a pending shortage and take one or more actions that prevent the potential shortage from occurring at that time. Officials noted that while a pending shortage may be prevented at one time, the drug could still go into shortage later. Thus, in a given year, a drug could be counted both as a potential shortage prevented and as an actual shortage. FDA officials also said there could be a second pending shortage of a drug in a given year. If FDA takes another action that prevented the shortage, it would count as two potential shortages prevented of the same drug for the year. For our analysis, this would count as one potential shortage prevented.

⁹³Consistent with the matter for Congressional consideration contained in our 2011 report, FDASIA required manufacturers to notify FDA at least 6 months prior to the date of a discontinuance or interruption (or as soon as possible if 6 months notice is not feasible) in the manufacture of a drug that is life supporting, life sustaining, or used to treat debilitating health issues. FDASIA required FDA to issue a final rule implementing this requirement by January 9, 2014. § 1001(a), 126 Stat. at 1099 (to be codified at 21 U.S.C. § 356c). FDA issued a proposed rule on November 4, 2013, with a 60-day comment period. 78 Fed. Reg. 65904 (Nov. 4, 2013) (to be codified at 21 C.F.R. pts. 20, 310, 314, and 600).

proactive and successful in its efforts. FDA officials noted there has been a sizeable increase in notifications with a six-fold increase after issuance of the drug shortages Executive Order in October 2011, a subsequent doubling of that rate after the enactment of FDASIA in July 2012, and a return to the Post-Executive Order notification rate in 2013.

FDA has expedited a number of agency actions to prevent or resolve shortages, in accordance with relevant FDASIA provisions. For example, FDA may expedite the review of ANDAs, or supplements to NDAs and ANDAs, to help bring an alternative drug to market or authorize an additional API supplier or manufacturing site.⁹⁴ FDA officials said the agency has also expedited inspections to facilitate improvements at manufacturing establishments. Expediting inspections that are required before an ANDA or supplement is approved also facilitates the availability of a needed drug. Manufacturer representatives we spoke with noted that in some cases expedited reviews or inspections have happened quickly and have helped prevent shortages. However, others told us that some application reviews or inspections have taken a long time, limiting the manufacturers' ability to help prevent or resolve a shortage. For example, one manufacturer representative said waiting for FDA's approval of ANDA supplements related to new raw material suppliers has been a key hindrance to the manufacturer's ability to respond to drug shortages.

In addition, FDA routinely contacts manufacturers regarding their ability to increase production in response to a potential or actual drug shortage. Although a number of manufacturer representatives said that ramping up production takes time and may not always be possible, given production capacity constraints, FDA has reported some successes. For example, when FDA determined that an impending product discontinuation might result in a shortage of a drug that treats shingles and chickenpox, it encouraged another manufacturer to increase production, thus avoiding a shortage. Similarly, when quality problems were identified in a drug used to treat eye infections in patients with acquired immune deficiency syndrome, FDA reached out to another manufacturer that was able to

⁹⁴According to FDA, between January 1, 2011, and June 30, 2013, the agency expedited 161 ANDAs, 97 ANDA supplements, and 38 NDA supplements in response to drug shortages; the number of expedited reviews may exceed the number of shortages reported because multiple applications or supplements may be expedited to alleviate a shortage. FDA reported to us that expedited review helped to prevent 211 potential shortages and helped to resolve 27 shortages.

increase production to avert a potential shortage. Manufacturer representatives said manufacturers will generally increase production, if possible, when FDA advises them of a shortage. FDA reported to us that, from January 1, 2011, to June 30, 2013, its encouragement to manufacturers to increase production helped prevent or resolve 41 shortages.

FDA officials said that in appropriate cases, the agency may attempt to use its regulatory discretion to keep products from going into short supply or from making an active shortage worse. FDA may use its discretion in deciding whether to take a certain action. FDASIA requires FDA to consider whether an enforcement action or issuance of a warning letter could reasonably cause or exacerbate a shortage of a life-saving drug.⁹⁵ If FDA reaches such a determination, the agency must evaluate the risks associated with the impact of such a shortage upon patients and the risks associated with the violation before taking action, unless there is an imminent risk of serious health consequences or death. FDA officials said that they had used their regulatory discretion prior to the enactment of FDASIA and were continuing to do so, through communication across various FDA offices and with manufacturers. Officials noted that they try to balance the risk to patients when making their decisions. That is, they consider the risk of allowing the continued distribution of the product—despite the problems related to the possible enforcement action or warning letter—against the public health risks of the product not being available. FDA officials said they also continue to use their regulatory discretion to temporarily allow the importation of “unapproved drugs” into the United States to help prevent or resolve shortages of FDA-approved drugs that are critical to patients, in rare cases where the shortages cannot be resolved by manufacturers willing and able to supply the FDA-

⁹⁵FDASIA defines a life-saving drug as one that is life-supporting, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition. § 1001(a), 126 Stat. at 1099 (to be codified at 21 U.S.C. § 356c(a)).

approved drugs in the immediate future.⁹⁶ We previously reported that FDA had allowed for the importation of seven unapproved drugs from January 2011 through September 2011. FDA officials told us that, through June 30, 2013, they have subsequently allowed for the importation of nine additional unapproved drugs.⁹⁷ For example, when the manufacturer of a drug used to treat patients who require total parenteral nutrition lost the use of a manufacturing site, FDA allowed importation of a comparable version of the drug not approved by FDA to prevent a potential shortage from occurring.⁹⁸

Several stakeholders commented that FDA's efforts to allow the importation of unapproved drugs to address a shortage have improved, which has helped to resolve some critical shortages. However, some stakeholders noted that certain shortages could not be resolved quickly because it took a long time for FDA to respond to providers' requests to allow importation. For example, some stakeholders noted that delays in the importation of total parenteral nutrition products created significant challenges for treating patients who depend upon them. To help speed up the process of temporary importation, FDA officials said that since January 2012 they have proactively identified foreign manufacturers that have expressed a willingness to import their drugs to help with a

⁹⁶Federal law directs FDA to review samples of drugs being imported into the United States from facilities that are not registered with the agency, and, if it identifies any such drugs as unapproved, to refuse entry of the drug into the country. 21 U.S.C. § 381(a). By not objecting to the entry of certain unapproved drugs to address a shortage, FDA effectively allows the importation and distribution of such drugs, but only under specified, controlled circumstances, and only after review of the manufacturer. FDA officials told us it is evaluating the potential impact of a recent decision issued by the U.S. Court of Appeals for the District of Columbia enjoining FDA from effectively allowing importation of an unapproved drug used by some states to administer a lethal injection on its management of drug shortages. In deference to law enforcement agencies, FDA had not objected to the drug being imported for use in lethal injections. See *Cook v. FDA*, 733 F.3d 1 (D.C. Cir. 2013).

⁹⁷According to FDA, the agency attempted to use this strategy in seven other instances, but could not do so. In four instances, FDA could not find a manufacturer willing and able to import the product into the United States to address the shortage. In the other three instances, FDA identified a manufacturer, but the shortage was already being resolved and importation was no longer necessary.

⁹⁸Total parenteral nutrition products—including protein, minerals, and vitamins—are administered intravenously to patients who cannot eat or absorb nutrients through other methods.

shortage. Officials said this has allowed them to reach out to companies more quickly and has already helped the agency address one shortage.

FDA has also reported using its regulatory discretion in other ways. For example, the manufacturer of a drug that may slow the progress of the human immunodeficiency virus and acquired immune deficiency syndrome lost its component supplier and was forced to find a new one. However, this new supplier was experiencing a quality problem. FDA used its regulatory discretion to allow the manufacturer to use the new component supplier while quality problems were being addressed after it determined those issues posed no significant risks to public health. In another instance, FDA used its regulatory discretion to allow the continued marketing of a drug, despite a manufacturing deviation, after determining the benefits of having the drug available outweighed the risk associated with the manufacturing error.

FDA Is Working to Further Improve Its Response to Drug Shortages

FDA is taking steps to further enhance its ability to respond to shortages. Some of the agency's actions are required by FDASIA, some are in response to recommendations we made in 2011, and others were initiated by the agency. For example, FDA has established the Drug Shortages Task Force as required by FDASIA.⁹⁹ FDA officials said the Drug Shortages Task Force has helped FDA revise internal policies and procedures, track the development of the proposed regulations for implementing the manufacturer notification requirements, and generally coordinate across the agency on issues related to drug shortages.

Consistent with other FDASIA requirements, FDA is continuing to make shortage information available to appropriate stakeholders, including physicians, patient groups, and DEA; is maintaining an up-to-date list of drugs in shortage; and has identified a mechanism through which health care providers and other groups report shortage-related information to FDA.¹⁰⁰ FDA officials told us the agency has been posting shortage information on its website since 1999 and includes information that

⁹⁹The Drug Shortages Task Force includes staff from the Office of Regulatory Affairs, the Center for Biologics Evaluation and Research, and a number of CDER offices, including the Office of the Center Director, the Office of Compliance, DSS, and the Office of Generic Drugs.

¹⁰⁰As required by FDASIA, FDA officials also noted that they have continued to work with DEA on shortages related to controlled substances.

describes how providers and others can report a potential drug shortage. The e-mail address and toll-free number listed on the website are the main mechanisms through which FDA receives drug shortage-related reports from health care providers or other third-party groups.

FDASIA requires FDA to maintain an up-to-date list of drugs that it determines to be in shortage and—subject to public health, trade secret, and confidentiality concerns—make the list publicly available. FDA officials told us that, upon receiving notification of a potential drug shortage, the agency works to verify whether a shortage exists through contacting the drug’s manufacturer to determine supply levels and comparing that to industry sales data on historical demand for the product. Once FDA determines that the amount of the drug—or pharmaceutical equivalents—appears to be insufficient to meet demand, the agency posts information about the shortage on its drug shortages website. Though FDA takes steps to respond to all shortages about which the agency is informed, officials said the agency places the highest priority on responding to shortages of drugs that it considers medically necessary.¹⁰¹ Nevertheless, officials said that FDA’s website includes all verified shortages, regardless of whether the drug is determined to be medically necessary.¹⁰² However, FDA officials noted that the agency may not be notified of all potential shortages, because FDASIA only requires manufacturers to report disruptions in the production of drugs that are life supporting, life sustaining, or used to treat debilitating health issues. Though health care professionals can also notify FDA about potential shortages, FDA officials told us that the agency is less likely to be notified about shortages of drugs for which there are easy substitutes or little patient impact.

¹⁰¹FDA defines a medically necessary drug as any drug that is used to treat or prevent a serious disease or medical condition for which there is no other adequately available drug that is judged by medical staff to be an appropriate substitute. For more on this determination, see [GAO-12-116](#); 27 and 47.

¹⁰²We previously found that FDA posted all shortages of medically necessary drugs, but only posted some shortages of non-medically necessary drugs, generally those for which FDA received multiple requests for information. FDA officials told us that they recently changed their approach when they began receiving more notifications about drug shortages as a result of the Executive Order and, later, FDASIA. Officials said that for the past 2 years, FDA has posted all shortages that the agency verifies, regardless of whether the drug is medically necessary.

In July 2012, as required by FDASIA, FDA began classifying the reasons for shortages using standardized terminology specified in the law and posting this information on its website along with information on estimated shortage duration.¹⁰³ Also, though not required by FDASIA, in July 2013 FDA added information on the therapeutic categories of drugs in shortage to its drug shortages website. This change allows users, for example, to view all oncology shortages in one place, rather than having to review the entire list of drugs in shortage and identify individual drugs used in oncology themselves. FDA plans to improve the functionality of the website further by allowing users to sort shortages by other types of information as well. A number of stakeholders noted that the improvements to FDA's drug shortage website help them keep informed about drug shortages. However, some expressed disappointment with the passive nature of the website as stakeholders must proactively visit the website as opposed to receiving automated alerts. A number of stakeholders noted that notifications of shortages by therapeutic class would be particularly helpful for communicating the potential for a shortage to targeted groups earlier. FDA officials said that they plan to add active alerts by therapeutic category to the website.

Although FDA continues to refine the information on its website, it is nonetheless dependent on what manufacturers report to the agency: the reported reasons for a shortage and the estimated length of the shortage. The information FDA receives from manufacturers and other sources may be incomplete and may change over time. As a result, the information on the website may not always be current and accurate. Stakeholders noted that the reasons given for the shortages are often categorized as "other" which can make it difficult to understand why a drug is in shortage. FDA officials said they use the category "other" when none of the classifying terminology required by FDASIA directly applies, although FDA officials said they try to include available details to help explain the cause of the shortage. In addition, FDA may not be able to publicly post all of the information the agency receives from manufacturers because some of the information provided to FDA is proprietary. Although some stakeholders reported that information on the duration of a shortage is one of the most useful pieces of information that can be provided, others noted that the

¹⁰³The reasons included in FDASIA are: requirements related to complying with good manufacturing practices, regulatory delay, shortage of an active ingredient, shortage of an inactive ingredient component, discontinuation of the manufacture of the drug, delay in shipping, and increased demand.

estimated shortage resolution dates on FDA’s website are not always reliable. Two stakeholders said that the estimated duration for a shortage is often listed as “unavailable” or “to be determined,” which is not particularly helpful. Stakeholders noted that such inaccuracies may limit their ability to plan ahead. For example, a representative of one provider group noted that in order to plan for the multiple rounds of a patient’s chemotherapy regimen, the provider would need to be sure that there will be a sufficient supply of the drug for the second round of chemotherapy before starting the first. Manufacturer representatives said the complexity of a manufacturing disruption often makes it difficult to provide FDA accurate estimates of the time it will take to resolve the disruption.

FDA has also taken steps to respond to the recommendations we made in our 2011 report. In response to our recommendation that FDA develop an information system that would allow drug shortage data to be tracked in a systematic manner—to be consistent with the internal control standards for the federal government—the agency developed a drug shortage database that is used on a daily basis to track shortages, document the actions FDA takes to prevent and resolve shortages, and monitor the workload of DSS personnel.¹⁰⁴ All FDA offices can access the database; however, the officials we spoke with said they request information from DSS instead of accessing the database directly.¹⁰⁵ In September 2013, FDA informed us that it is now planning to transition from its existing database to an information system with additional capabilities and functionality. For example, FDA officials said they are planning to automate some of the data fields by extracting information from other sources that provide NDCs, market share, and other relevant product information. This may reduce the likelihood of manual entry errors and speed up the entry of some shortage information. The officials said the establishment of an information system could also help facilitate analysis related to drug shortages. However, they were unable to provide us with a description of the types of analyses they would conduct.

¹⁰⁴GAO-12-116, 44. See GAO/AIMD-00-21.3.1, 19.

¹⁰⁵FDA officials said the database will also be used to prepare the annual drug shortages report to Congress, as required by FDASIA. The first annual report was due by the end of calendar year 2013.

FDA has also taken steps to respond to our recommendation related to the resources allocated to the drug shortage program.¹⁰⁶ FDA has since increased the number of DSS personnel from 4 in 2011 to 11 in 2013 and officials said this has improved FDA's ability to respond to drug shortages in a number of ways. First, it allowed FDA to assign each manufacturer experiencing a shortage a specific contact person, which FDA officials said has allowed the agency and the manufacturers to develop better working relationships and has improved information sharing. Representatives from one manufacturer we spoke with agreed that this effort has improved their relationship with FDA. In addition, a number of stakeholders, including other manufacturers' representatives, noted it is now easier to contact DSS officials and that discussions have become more regular. Second, FDA officials said having additional staff has allowed them to respond more quickly to manufacturer notifications and to identify possible approaches to preventing or resolving a shortage. Some stakeholders also noted that FDA reached out to them for additional information on specific drug shortages or the availability of certain drugs. Third, officials said it has allowed DSS to play a bigger role in revising drug shortage policies and procedures.

FDA also improved the staffing resources available for responding to drug shortages by assigning drug shortage coordinators in each of its 20 district offices. In addition, it developed written procedures to enhance coordination between headquarters staff in DSS, the CDER Office of Compliance, and staff in the district offices on issues related to drug shortages.¹⁰⁷ FDA officials told us that the drug shortage coordinators have helped bring drug shortage-related concerns to light earlier, such as violative inspections at establishments that manufacture a large volume of drugs. Officials said this has improved FDA's ability to work with such

¹⁰⁶In 2009, we found that FDA faced challenges fulfilling and managing its growing medical product oversight responsibilities, which agency officials said was due to resource constraints, and we recommended that FDA conduct a comprehensive assessment of the agency's staffing resources. See GAO, *Food and Drug Administration: FDA Faces Challenges Meeting Its Growing Medical Product Responsibilities and Should Develop Complete Estimates of Its Resource Needs*, [GAO-09-581](#) (Washington, D.C.: June 19, 2009). Consistent with the 2009 recommendation, in 2011 we recommended that FDA assess the resources allocated to the Drug Shortage Staff to determine whether reallocation is needed to improve the agency's response to drug shortages. See [GAO-12-116](#), 43.

¹⁰⁷Food and Drug Administration, *Product Shortage Communication*, Field Management Directive No. 15, (July 31, 2012).

manufacturers early in order to prevent drug shortages. FDA held a retreat in July 2012 to educate the drug shortage coordinators and other staff on FDA's processes for responding to drug shortages. The retreat included a number of FDA offices, including CDER Office of Compliance, DSS, Office of Generic Drugs, Office of New Drug Quality Assessment, and Office of Regulatory Affairs, and officials said the retreat helped attendees understand drug shortage responsibilities of the various FDA offices.¹⁰⁸

As required by FDASIA, FDA's Drug Shortages Task Force developed a strategic plan that identifies its goals and priorities for mitigating and resolving ongoing shortages and for preventing future shortages. This is also in line with our 2011 recommendation that FDA ensure that the agency's strategic plan articulates goals and priorities for maintaining the availability of all medically necessary drugs. Though FDA officials said the agency has not made this change in the agency-wide strategic plan, FDA's drug shortages strategic plan includes two goals related to maintaining drug availability, each with a number of tasks for achieving the goal. The first goal—to improve and streamline FDA's current mitigation activities once the agency is notified of a supply disruption or shortage—includes four tasks: streamline internal FDA processes; improve data and response tracking; clarify roles and responsibilities of manufacturers; and enhance public communication about drug shortages. The second goal—to develop prevention strategies to address the underlying causes of production disruptions to prevent drug shortages—contains three tasks: develop methods to incentivize and prioritize manufacturing quality; use regulatory science to identify early warning signals of shortages; and increase knowledge to develop new strategies to address shortages. As part of this second goal, the strategic plan describes efforts FDA is considering to help address manufacturing and quality issues, including broader use of manufacturing metrics to assist in the evaluation of manufacturing quality and developing incentives for high-quality manufacturing.

¹⁰⁸Currently FDA documents the responsibilities and procedures of the various offices in relation to drug shortages in its Manual on Policies and Procedures, section 6003.1. FDA officials told us that they are currently working on updating these policies and procedures (last revised in February 2012) but do not have an estimated timeframe for the completion of the revisions.

Finally, FDA officials said that their annual report on drug shortages, which was due December 31, 2013, will contain information on performance measures to assess and quantify the implementation of the agency's goals and response to drug shortages, as we recommended in 2011. As of January 31, 2014, the annual report has not been released.

FDA Lacks Policies and Procedures for Its Use and Management of Drug Shortage Data

While FDA is planning on establishing a new information system to track drug shortage data, it lacks policies, procedures, and specific training materials related to management and use of its existing drug shortage database. While FDA did create a database glossary, which briefly defines a number of the data fields, an official told us that no other documents or training materials have been created because staff use the existing database every day and are therefore familiar with its operation. Further, while FDA officials said they plan to create policies for entering data in the planned new drug shortage information system and create a tutorial for users, they have not yet done so. This lack of documentation may limit the agency's ability to communicate proper use of the existing and new databases to staff and could also ultimately lead to inconsistencies in the use of the database. The lack of policies and procedures is also inconsistent with internal control standards for the federal government, which state that agencies should have controls over information processes, including procedures and standards to ensure the completeness and accuracy of processed data.¹⁰⁹ For example, internal controls require the appropriate documentation of system controls and that such documents be readily available for review. Such documentation may include management directives, administrative policies, and operating manuals; none of which have been prepared for the existing database.¹¹⁰

Related to FDA's lack of policy and procedures for its existing drug shortage database, we also found that FDA lacks sufficient controls to ensure the quality of the data in the existing database. For example, FDA officials said there are no automated data checks to ensure the accuracy of the data in the database. Instead, officials review the data for accuracy at the end of each year by relying on their memories of events, emails, and meeting notes. The first such data check was completed in 2012.

¹⁰⁹GAO/AIMD-00-21.3.1.

¹¹⁰GAO/AIMD-00-21.3.1.

Officials said they plan to perform another such review at the end of 2013, in preparation for the annual report to Congress. This practice is inconsistent with the internal control standards for the federal government, which require agencies to design controls, which may include data checks that help ensure completeness, accuracy, and validity of database entries. Without such data checks, FDA's existing database may be more likely to have errors, incomplete data, and inconsistent data. We asked officials to provide us with any documentation of their 2012 review of the existing database for accuracy and they were unable to do so. FDA officials said they plan to incorporate automated data checks in their new information system, which may eliminate the need for subsequent manual quality checking. FDA officials told us that, as of January 2014, any new drug shortages will be entered into their new information system.

In addition, FDA has not conducted routine analyses of its existing drug shortage database to identify, evaluate, and respond to the risks of drug shortages proactively. Again, according to the internal control standards for the federal government, agencies should comprehensively identify risk through qualitative and quantitative methods, including data collected in the course of their work.¹¹¹ FDA's drug shortages strategic plan states that the agency will explore using risk-based approaches to identify early warning signs of problems that could lead to production disruptions. However, FDA currently uses data on an ad hoc basis to respond to specific shortages as opposed to using the data to identify trends or patterns that may help it predict and possibly prevent shortages. According to FDA officials, other than producing the annual report required by FDASIA, the agency has not established regular schedules for generating reports in the database and is not currently using the database to conduct regular trend analyses. By only using the database to respond to individual shortages as they occur, FDA is missing opportunities to use the data proactively to enhance the agency's ability to prevent and mitigate drug shortages.

Conclusions

FDA has made progress in preventing potential drug shortages and responding to actual shortages since we issued our last report in 2011. In part, this progress can be attributed to the new FDASIA requirement that

¹¹¹[GAO/AIMD-00-21.3.1](#).

manufacturers provide FDA with information about potential or current shortages of drugs that are life supporting, life sustaining, or used to treat debilitating health issues. This additional information has improved the agency's ability to act more quickly when it learns of a potential shortage. Yet, the number of shortages remains high, despite the fact that FDA has taken steps to prevent and mitigate shortages, such as expediting application reviews and inspections, exercising enforcement discretion in appropriate cases, and helping manufacturers respond to quality problems. Many shortages are prolonged, with some spanning multiple years. As a result, patients and providers continue to struggle as essential and life-saving medications—such as anti-infective, nutritive, and cardiovascular drugs—remain in short supply. These shortages complicate patient care and may lead to adverse outcomes with serious consequences.

Although there are potential underlying causes of drug shortages, FDA has made important strides in responding to some immediate causes. However, some of the causes identified in our literature review and conversations with manufacturers are beyond the agency's authority, as it does not have control over private companies' business decisions. For example, FDA is unable to require manufacturers to start producing or continue producing drugs, or to build redundant manufacturing capacity, regardless of the severity of a shortage. Nonetheless, FDA can take steps to maximize the agency's ability to use the information at its disposal to address drug shortages. We continue to believe in the importance of our prior recommendation that FDA should develop an information system that would facilitate the agency's response to shortages. FDA took the first step in implementing this recommendation by creating a database on drug shortages. However, a key component of any system is assuring the reliability of the data. Our current work shows that the agency lacks adequate policies and procedures governing the use of its database, as well as sufficient checks to ensure the data's reliability—in both cases, the failure to do so is inconsistent with internal controls for the federal government. These shortcomings could hinder FDA's efforts to understand the causes of shortages as well as undermine its efforts to prevent them from occurring. Additionally, FDA's ability to manage risk-based decisions, including when to use regulatory discretion, and proactively help prevent and resolve shortages may be hindered by its lack of routine analysis of the data it collects. FDA may be missing an opportunity to identify causes of shortages, risks for shortages, and patterns in events which may be early indicators of shortages for certain types of manufacturers, drugs, or therapeutic classes. Though FDA has taken important steps to better prevent and address shortages, the large

number of potential shortages itself suggests a market still at risk of continuing supply disruptions.

Recommendations

To enhance its oversight of drug shortages, particularly as the agency fine-tunes the manner in which it gathers data on shortages and transitions from its database to a more robust system, we recommend that the Commissioner of FDA take the following two actions:

- develop policies and procedures for the use of the existing drug shortages database (and, ultimately, the new drug shortages information system) to ensure staff enter information into the database in a consistent manner and to ensure the accuracy of the information in the database; and
- conduct periodic analyses using the existing drug shortages database (and, eventually, the new drug shortages information system) to routinely and systematically assess drug shortage information, and use this information proactively to identify risk factors for potential drug shortages early, thereby potentially helping FDA to recognize trends, clarify causes, and resolve problems before drugs go into short supply.

Agency and Third-Party Comments and Our Evaluation

We provided a draft of this report for comment to HHS, the Department of Justice, and the Federal Trade Commission. We also provided excerpts of this report for comment to the Department of Defense, the Department of Homeland Security (for review of the U.S. Coast Guard), the Department of Veterans Affairs, and UUDIS. We received written comments from HHS, which are reproduced in appendix V. We also received technical comments from HHS, the Department of Defense, the Federal Trade Commission, and UUDIS, which we incorporated as appropriate. The Department of Homeland Security, the Department of Justice, and the Department of Veterans Affairs did not have any comments based on their review.

In its comments, HHS stated that drug shortages remain a significant public health issue and emphasized its commitment to preventing new shortages and resolving those that are already ongoing. HHS agreed with our recommendations to enhance its oversight by developing policies and procedures for its drug shortages database and by conducting periodic analyses of these data to identify drug shortage risk factors. Regarding our first recommendation, HHS said it agrees that policies and procedures for data entry are important to help assure the timely,

accurate, and consistent inputting of data into its drug shortage database. Regarding our second recommendation, HHS agreed that it could make better use of its drug shortage data to identify trends, clarify causes of shortages, and resolve problems before drugs go into short supply. However, HHS noted that there are many factors that can trigger or exacerbate a shortage and that it lacks some relevant data, such as detailed information on manufacturing capability, to create a comprehensive forecasting system for drug shortages. We acknowledge that the agency's access to certain information is limited, but believe that routine analysis of available data could nonetheless reveal some early indicators of shortages.

Although HHS agreed with our recommendations, it took issue with our use of UUDIS data concerning the persistence of recent shortages. HHS said that these data may overstate the number of shortages that persist because UUDIS considers a shortage to be ongoing unless all NDCs for a given product are available, even if some manufacturers that currently produce the drug have increased production enough to meet all demand. We recognize that there are differences in the way UUDIS and FDA define, and therefore count, shortages. Our report notes that FDA considers a shortage to be resolved when the total supply of the drug and any pharmaceutical equivalents is sufficient to meet demand in the market overall. UUDIS defines shortages more broadly, focusing on supply issues that affect how pharmacies prepare and dispense a product or that influence patient care when prescribers must choose an alternative therapy because of supply issues. According to a UUDIS official, tracking all NDCs for all manufacturers is important for providers because using substituting one package size for another may create a safety issue. To enhance clarity, we have provided additional detail in our report to describe UUDIS's methods for defining and tracking shortages.

Moreover, it is important to note that we used UUDIS data because FDA was unable to provide data on shortages that would allow for an analysis of trends. As we have previously reported, until FDA established a database containing shortage information in 2011, the agency did not systematically maintain data on shortages.¹¹² In the absence of FDA data, the data from UUDIS was the only data that we could identify that would allow for a meaningful analysis of drug shortages over time.

¹¹²See [GAO-12-116](#).

We are sending copies of this report to the Secretary of the Department of Health and Human Services, the Attorney General, the Chairman of the Federal Trade Commission, appropriate congressional committees, as well as other interested parties. In addition, the report is available at no charge on the GAO 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 crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who make key contributions to this report are listed in appendix VI.

A handwritten signature in black ink that reads "Marcia Crosse". The signature is written in a cursive style with a long horizontal line extending to the right.

Marcia Crosse
Director, Health Care

List of Addressees

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

The Honorable Fred Upton
Chairman
The Honorable Henry A. Waxman
Ranking Member
Committee on Energy and Commerce
House of Representatives

The Honorable Anna G. Eshoo
Ranking Member
Subcommittee on Communications and Technology
Committee on Energy and Commerce
House of Representatives

The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives

The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

The Honorable John D. Dingell
House of Representatives

The Honorable Edward J. Markey
United States Senate

Appendix I: Scope and Methodology - Trends in and Causes of Drug Shortages

As part of our report objectives, we reviewed the trends in recent drug shortages and examined the causes of drug shortages. This appendix provides further detail on our methods.

Trends

To review the trends in recent drug shortages, we identified the number of drugs that were in short supply from January 1, 2007, through June 30, 2013, and examined the characteristics of drugs that were reported to be in shortage from June 1, 2011, through June 30, 2013. Specifically, to review trends in recent drug shortages that occurred from January 1, 2007, through June 30, 2013, we analyzed data from the University of Utah Drug Information Service (UUDIS), which were the most recent data available at the time we did our work.¹ These data are generally regarded as the most comprehensive and reliable source of drug shortage information for the time period we reviewed and are what we used in preparing our 2011 report.² We focused our analysis on shortages of prescription drugs.³ We reviewed UUDIS' drug shortage data to identify (1) the total number of new shortages reported each year and (2) the total

¹UUDIS 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 the Food and Drug Administration (FDA) telling UUDIS that Manufacturers B and C have increased supply and all market need has been met.

²GAO, *Drug Shortages: FDA's Ability to Respond Should be Strengthened*, [GAO-12-116](#) (Washington, D.C.: Nov. 21, 2011), 2. At the time of our previous report, FDA did not have a database containing information on drug shortages for the time period we reviewed. Since the publication of that report, FDA has developed a database that it uses to track shortages. For the purposes of this report, we used the drug shortage data maintained by UUDIS because the time period reviewed included data from years that predate FDA's development of its database and to provide comparable information on the trends and characteristics of drug shortages to that which we presented in our 2011 report. In that report, we analyzed UUDIS data from January 2001 through June 2011.

³Shortages of over-the-counter drugs, biologics (including vaccines), medical devices, and orally-administered vitamins, which UUDIS also tracks, were excluded from our analysis.

number of active shortages each year. To calculate the total number of new shortages reported each year, we counted shortages only for the year in which UUDIS was first notified and not in any subsequent years during which the shortage may have been active.⁴ To calculate the number of active shortages in each year, we included both shortages reported that year and any shortages that had started in a prior year, but were still ongoing during the year.⁵ We also identified the duration of any shortages reported from January 1, 2007, through June 30, 2013, and the number of drugs that had been in short supply on more than one occasion. To identify drugs that had been in short supply more than once, we grouped together shortages of clinically interchangeable versions of a drug that were administered through the same route, such as injection. We confirmed our grouping of these shortages with a knowledgeable pharmacist from UUDIS.

To analyze the characteristics of shortages, we reviewed 219 drug shortages that were newly reported between June 1, 2011, and June 30, 2013, and that UUDIS identified as critical.⁶ These critical shortages were a subset of the total number of shortages reported during this time. Specifically, these 219 shortages represented 57 percent of the 382 shortages reported between June 1, 2011, and June 30, 2013. UUDIS identified these shortages as critical because alternative medications were unavailable, the shortages affected multiple manufacturers, or it received multiple reports from different institutions. For these critical shortages, we obtained drug shortage bulletins created by UUDIS, which contain the national drug codes (NDC) associated with each shortage.⁷

⁴For example, a shortage reported in July 2010 and resolved in March 2012 would have been counted in the total for reported shortages in 2010, but not in either 2011 or 2012.

⁵For example, a shortage reported in July 2010 and resolved in March 2012 would have been counted in the active shortage total in three different years, 2010—the year in which it was reported—and 2011 and 2012—years in which it was still ongoing.

⁶In our previous report, we examined the characteristics of 269 critical drug shortages that were reported from January 1, 2009, through June 20, 2011. See [GAO-12-116](#), 2.

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 NDCs associated with the shortage. A NDC is a unique identifier, though one drug can have multiple NDCs associated with it. For example, a drug made by one manufacturer, in one strength, but in three package sizes would have a different NDC for each of the three package sizes. UUDIS does not consistently track the NDCs associated with shortages that it has determined are not critical.

Using these NDCs, we analyzed Red Book data to determine the product types, routes of administration, and therapeutic classes of the critical shortages.⁸ We reviewed all UUDIS data for reasonableness, outliers, and consistency, and determined that the data were sufficiently reliable for our purposes.

Causes

Literature Review

To examine the causes of recent drug shortages, we conducted a structured search of research databases using various combinations of relevant search terms including, “drug”, “shortage”, “supply”, “medication”, and “generic” to identify any literature published from January 1, 2003, through June 30, 2013, that reported on the causes of drug shortages.⁹ We then reviewed the abstracts for 714 articles and the full-text of 176 of those articles to determine whether they addressed the causes of drug shortages and met our inclusion criteria. Our inclusion criteria included journal articles and government publications, as well as policy briefs or papers, in which the causes of drug shortages were examined through the presentation of original research. Because there is not a large volume of peer-reviewed literature that incorporates original research, we also included articles that provided an in-depth discussion of the causes of drug shortages. However, we excluded editorials and news wire articles from our review. Finally, we included directly relevant studies to which we were referred by stakeholders, but which did not appear in our initial search. Based on these steps, we identified 20 articles that were published between March 1, 2005, and March 31, 2013, and then summarized the causes of shortages on which these articles reported.¹⁰ While our search criteria were for shortages of all drug types, the majority of the articles we identified were focused on generic sterile injectables, which have frequently been in shortage in recent years. For the purposes of reporting on our literature review, we identified and summarized the causes frequently discussed in the literature and did not list all topics

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

⁹We searched multiple bibliographic databases, including ProQuest, MEDLINE, Embase and SciSearch among others.

¹⁰For the purposes of this report, we did not independently validate the findings regarding the causes of drug shortages reported in literature included in our review.

mentioned in each article we reviewed. Some causes that were mentioned only sparingly in the literature were not included in our review.

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Stakeholder Views

We also interviewed, and in some cases, obtained written responses from, manufacturers and group purchasing organizations (GPO) regarding the causes of drug shortages identified through our literature review because the reported causes we identified were related to the role that these stakeholders have in the drug supply chain.¹¹ We interviewed three leading national associations representing drug manufacturers, both brand-name and generic, and five generic sterile injectable manufacturers. Specifically, we selected the top three manufacturers of generic sterile injectables between 2010 and 2012. We also selected two additional manufacturers, which were among the manufacturers associated with the highest number of shortages, according to a 2011 report by the IMS Institute for Healthcare Informatics.¹² We provided manufacturers and manufacturer associations with a list of potential causes based on our review of the literature and asked them to comment on each cause either through interviews or in writing. Finally, we selected the three largest GPOs based on their self-reported purchasing volume in fiscal year 2011 and asked each to comment on causes in writing.¹³

Analysis of FDA Data

We also analyzed FDA data on the reported causes of shortages for all shortages that it was notified about from January 1, 2011, through June 30, 2013. All data came from the database that FDA has developed to track shortages and reflects information reported by manufacturers to FDA that is subsequently analyzed and categorized by the agency. FDA defines a shortage as when the total supply of a drug and any pharmaceutical equivalents is inadequate to meet demand.¹⁴ FDA's definition of a shortage differs from UUDIS' and UUDIS also tracks shortages that do not meet FDA's definition of a shortage. For example, according to FDA officials, UUDIS will track shortages that only affect one

¹¹GPOs negotiate purchasing contracts with drug manufacturers and distributors, among other suppliers, on behalf of hospitals and other health care providers.

¹²IMS Institute for Healthcare Informatics, *Drug Shortages: A Closer Look at Products, Suppliers, and Volume Volatility*. (Parsippany, NJ.: November 2011).

¹³For the purposes of this report, we did not request documentation to independently validate the testimonial information regarding the causes of drug shortages that was reported by representatives from manufacturers and GPOs. In subsequent work, we intend to further explore the causes of drug shortages.

¹⁴A pharmaceutical equivalent is a drug product that is identical in dosage form, active pharmaceutical ingredient (API), and strength, and delivers an identical amount of API over an identical dosing period. See 21 C.F.R. § 320.1(c) (2013).

manufacturer, even if other manufacturers of the same drug have supply available. FDA, however, will not consider such a situation to be a shortage if the other manufacturers that can supply the drug can meet national demand. We interviewed FDA Drug Shortages Staff about the data and reviewed it for reasonableness, outliers, and consistency, and for our purposes, we determined that the data were sufficiently reliable.

Appendix II: List of Organizations Interviewed

Federal Agencies

1. Centers for Medicare & Medicaid Services
2. Department of Defense
3. Department of Justice
4. Department of Veterans Affairs
5. Federal Trade Commission
6. Food and Drug Administration
7. Indian Health Service
8. National Institutes of Health
9. Office of the Assistant Secretary for Planning and Evaluation, Department of Health and Human Services
10. U.S. Coast Guard

Provider Organizations

1. American Academy of Pediatrics
2. American College of Clinical Pharmacy
3. American Hospital Association
4. American Medical Association
5. American Pharmacists Association
6. American Society for Parenteral and Enteral Nutrition
7. American Society of Clinical Oncology
8. American Society of Health-System Pharmacists
9. Children's Hospital Association
10. National Community Pharmacists Association

Wholesale Distributors

1. AmerisourceBergen Corporation
2. Cardinal Health
3. McKesson Corporation

**National
Manufacturer
Associations**

1. Biotechnology Industry Organization
2. Generic Pharmaceutical Association
3. Pharmaceutical Research and Manufacturers of America

Manufacturers

1. APP, a division of Fresenius Kabi USA, LLC
2. Ben Venue Laboratories, Inc.
3. Hospira, Inc.
4. Teva Pharmaceuticals USA
5. West-Ward Pharmaceuticals

**Group Purchasing
Organizations**

1. MedAssets
2. Novation, LLC
3. Premier, Inc.

Other Groups

1. Healthcare Supply Chain Association
2. International Association of Fire Chiefs
3. Institute for Safe Medication Practices
4. National Association of Medicaid Directors
5. Oley Foundation
6. Physicians Against Drug Shortages
7. Safety Net Hospitals for Pharmaceutical Access

Appendix III: Steps Federal Agencies Have Taken to Respond to Gray Market Activities

In the event of a drug shortage, providers who are unable to obtain drugs from their regular wholesale distributors may resort to purchasing drugs through distribution channels that were not authorized by the manufacturer, referred to as the gray market.¹ Gray market suppliers typically obtain small quantities of a drug that is in short supply and offer it for purchase at an inflated price.² Because the origin of gray market drugs may be unknown, there is no guarantee of the drug's pedigree or assurance that it was stored and transported appropriately, potentially putting patients at risk.³

This appendix describes steps federal agencies have taken in response to activities associated with the gray market for shortage drugs. To identify steps that federal agencies have taken, we interviewed officials from FDA, the Department of Justice (DOJ), and the Federal Trade Commission (FTC); reviewed federal laws and regulations, including an Executive Order on reducing prescription drug shortages issued on October 31, 2011; and examined agency documents.

¹Specific wholesale distributors may serve as an "authorized distributor of record" for a given manufacturer. Authorized distributor of record agreements may obligate a wholesale distributor to only purchase a manufacturer's products directly from the manufacturer and to only sell those products to hospitals and pharmacies.

²A survey by Premier, Inc., a group purchasing organization, found that prices being offered for shortage drugs during a 2-week period at the beginning of 2011 were on average 650 percent greater than Premier's contract price, and ranged up to 4,533 percent greater than their contract price. See Premier, Inc., *Buyer Beware: Drug Shortages and the Gray Market* (Charlotte, N.C., 2011). This is consistent with the results of a Congressional investigation, which found that gray market suppliers often charge exorbitant prices to health care providers for drugs facing critical shortages. See "Shining Light on the Gray Market: An Examination of Why Hospitals are Forced to Pay Exorbitant Prices for Prescription Drugs Facing Critical Shortages," Staff Report Prepared for Senator John D. Rockefeller IV, Chairman, Senate Committee on Commerce, Science and Transportation; Senator Tom Harkin, Chairman, Senate Committee on Health, Education, Labor, and Pensions; and Representative Elijah E. Cummings, Ranking Member, House Committee on Oversight and Government Reform. (Washington, D.C.: July 25, 2012).

³A drug pedigree is a statement of origin that identifies each prior sale, purchase, or trade of a drug, including the date of those transactions and the names and addresses of all parties to them.

Federal Role in Relation to
the Gray Market for
Shortage Drugs

Among other things, the October 31, 2011, drug shortages Executive Order directed FDA to communicate to DOJ any findings by FDA that shortages have led market participants to stockpile shortage drugs or sell them at exorbitant prices.⁴ The Executive Order also directed DOJ to determine whether these activities violate federal law, and if so, to take appropriate enforcement actions.

Certain activities involved with the sale of shortage drugs on the gray market could violate federal law—namely, the Federal Food, Drug, and Cosmetic Act (FDCA) and federal antitrust laws. Working together, FDA and DOJ are responsible for investigating and prosecuting violations of the FDCA, including provisions prohibiting counterfeiting and noncompliance with drug pedigree requirements. Under the FDCA, FDA is responsible for ensuring the safety, effectiveness, and quality of domestic and imported prescription drugs. This includes developing standards and identifying and validating effective technologies to secure the drug supply chain against counterfeit and diverted drugs.⁵ Among other requirements, the FDCA requires that drugs meet purity and quality standards, are authentic, and are stored under proper conditions. In addition, the FDCA requires a drug's path through the supply chain to be documented through a drug pedigree.⁶ FDA may take certain administrative actions against those that manufacture, market, or sell

⁴Exec. Order No. 13,588, reprinted at 3 C.F.R. 281 (2012).

⁵21 U.S.C. § 355e. Counterfeit drugs, which are defined in law at 21 U.S.C. § 321(g)(2), include, for example, those sold under a product name without proper authorization—where the drug is mislabeled in a way that suggests that it is the authentic and approved product—as well as unauthorized generic versions of FDA-approved drugs that mimic trademarked elements of such drugs. Diverted drugs are legitimate drugs that are illegally bought, sold, or otherwise circulated outside of the legal distribution system that has been established to ensure safety and quality. Diversion can involve such activities as illegal sales of prescription drugs by physicians, patients, or pharmacists; prescription forgery; or pharmacy theft.

⁶21 U.S.C. § 353(e).

drugs that violate FDCA requirements. DOJ, often in consultation with FDA, may bring civil and criminal actions for such violations.⁷

FTC and DOJ's Antitrust Division are responsible for enforcing federal antitrust laws, which are designed to preserve and protect market competition.⁸ The federal antitrust laws include the Sherman Act, the Federal Trade Commission Act, and the Clayton Act. The Sherman Act, enforced by DOJ, prohibits monopolization and restraints of trade, and civil and criminal penalties may be imposed for violations of the act.⁹ The Federal Trade Commission Act, enforced by FTC, bans unfair methods of competition and unfair or deceptive acts or practices.¹⁰ For example, collusion by drug manufacturers to set prices may violate both the Sherman Act and the Federal Trade Commission Act. The Clayton Act, jointly enforced by DOJ and FTC, regulates mergers and acquisitions and prohibits those that may substantially lessen competition or create a monopoly and are, therefore, likely to increase prices for consumers.¹¹ The Federal Trade Commission Act and Clayton Act are civil statutes that do not carry criminal penalties.

Depending on the circumstances, there could be other authorities under which federal agencies could investigate and prosecute gray market

⁷Legislation enacted in November 2013 mandates the establishment over the next 10 years of a national interoperable, electronic system to track certain prescription drugs through the supply chain that is intended, among other things, to protect against counterfeit and diverted drugs. Drug Quality and Security Act, Pub. L. No. 113-54, tit. II, 127 Stat. 587, 599 (2013). The law also requires manufacturers and repackagers to package certain prescription drug products with a product identifier within 4 or 5 years, respectively. It also requires wholesale distributors and dispensers to accept and dispense only prescription drug products with such product identifiers, within 6 or 7 years, respectively. In addition, the law requires manufacturers, wholesale distributors, repackagers, and dispensers to implement a system, by January 1, 2015, to help ensure products are not counterfeit, diverted, stolen, the subject of a fraudulent transaction, or otherwise unfit for distribution, and restricts all such entities from purchasing or selling a drug to entities that meet certain federal and state requirements. Violations of these provisions may result in criminal penalties or, in some cases, civil remedies, such as seizure, under the FDCA.

⁸FTC only has the authority to investigate civil antitrust cases. If the case is criminal in nature, FTC refers it to DOJ.

⁹See 15 U.S.C. §§ 1-7.

¹⁰See 15 U.S.C. §§ 41-58.

¹¹See 15 U.S.C. §§ 12-27.

activities. This includes, for example, the mail fraud statute, which makes it a crime to use the U.S. mail to commit a fraud, such as facilitating the sale of a shortage drug with a fake pedigree through the U.S. mail.¹²

Federal Agencies Review Gray Market Complaints for Illegal Activity

Consistent with the October 31, 2011, Executive Order on drug shortages, three federal agencies—FDA, DOJ, and FTC—review information concerning possible gray market sales of shortage drugs from a number of sources and have taken other steps to respond to relevant directives contained in the order.¹³ Yet officials from all three federal agencies told us that their authorities in relation to the gray market are limited. They explained that the selling of shortage drugs by suppliers not authorized by the manufacturer alone, even at exorbitant prices, does not itself violate federal law. Though gray market sales may violate agreements between manufacturers and wholesale distributors, such sales may not violate federal law unless they are made outside the legal distribution system. As a result, there have been no prosecutions or enforcement actions taken by federal agencies solely on the basis of gray market activities.

FDA has compiled gray market solicitations into quarterly reports that it shares with DOJ as part of its response to the Executive Order's directive to communicate findings that shortages have led to the stockpiling or sale of shortage drugs at exorbitant prices.¹⁴ From January 2012—when FDA first began providing this information to DOJ—through October 2013, FDA shared information on solicitations from 26 different wholesale distributors. According to FDA officials, these solicitations typically originate as e-mails to providers containing advertisements that list the drugs for sale and, in some cases, the prices, which the providers then forward to FDA. FDA officials said that some of the gray market solicitations were for sterile injectables in shortage, including drugs related to cancer treatment, emergency medicine, antibiotics, and

¹²See 18 U.S.C. § 1341.

¹³Exec. Order No. 13,588, reprinted at 3 C.F.R. 281 (2012). Although FTC was not specifically identified in the Executive Order, the agency is responsible for enforcing federal antitrust laws and has undertaken activities to respond to the order.

¹⁴Although the origin of gray market drugs is unclear, some commentators suggest that gray market vendors hoard or stockpile a drug if the vendor suspects an impending shortage and later sell the drug at an inflated price.

nutritive products. For example, one solicitation stated that a wholesale distributor was offering an intravenous multi-vitamin for \$785, when the average wholesale price for that same vitamin was \$8.61.

FDA officials told us that they review the solicitations to determine whether they violate the FDCA, such as a wholesale distributor making false claims about a drug or diverting a drug outside the legal distribution system. FDA has opened a number of investigations in relation to the solicitations to examine whether counterfeiting or diversion had occurred, but did not identify any illegal activity.¹⁵ For example, when the anesthetic propofol was in shortage, FDA did not object to the temporary importation of an unapproved version of the drug, but limited distribution to the manufacturer of the drug.¹⁶ However, in January 2010 FDA initiated two investigations related to complaints that the imported drug was being distributed by wholesale distributors, rather than the manufacturer. In both cases, FDA could not substantiate a criminal violation, so it closed the investigations. FDA officials told us that the FDCA does not prohibit hoarding or stockpiling of shortage drugs or regulate drug pricing. As a result, as of December 2013, FDA had not taken any enforcement action related to the gray market solicitations they reviewed, but had provided information from the solicitations to DOJ.¹⁷

¹⁵FDA officials told us that the agency does not track gray market investigations in a manner that would allow them to identify the total number of investigations with any certainty, but in response to our request, identified four such investigations that took place between January 2010 and January 2013.

¹⁶FDA may apply regulatory discretion to enhance the availability of drugs in shortage. In certain circumstances, FDA may not object to the temporary importation of drugs not approved by FDA for marketing in the United States, subject to appropriate controls. FDA officials explained that the agency's exercise of regulatory discretion does not mean that these products meet regulatory standards for approval, or that a manufacturer has a legal right to distribute them. Rather, FDA may decide not to object to the distribution of the drug for a limited time for public health reasons.

¹⁷In addition, prior to issuance of the Executive Order, FDA contracted for an analysis of online sales of shortage drugs. The contractor's analysis found evidence that, as of November 2011, 106 different websites were offering 67 drugs from FDA's shortage list for sale, with evidence of price gouging in 38 cases. FDA shared this analysis with DOJ. DOJ officials told us that they reviewed this report and have discussed the online sales of drugs by illicit pharmacy websites with FDA. Officials noted that DOJ has prosecuted the operators of such websites in recent years, regardless of whether they have sold drugs in shortage. For more on prosecutions of operators of rogue Internet pharmacies, see GAO, *Internet Pharmacies: Federal Agencies and States Face Challenges Combating Rogue Sites, Particularly Those Abroad*, [GAO-13-560](#) (Washington, D.C.: July 8, 2013).

Officials from DOJ told us that, as required by the Executive Order, they review FDA's quarterly reports for information that could indicate the drug listed was diverted for illegal purposes. For example, DOJ considers whether there is evidence of use of fake pedigrees in violation of the FDCA. DOJ officials noted that the solicitations listed in the quarterly reports sometimes indicate that a drug is being sold for a higher-than-normal price; however, selling drugs at elevated prices alone is not illegal. Such sales may be illegal, for example, if the drugs are bought and sold through diversion from the legal distribution system. DOJ officials told us that as of November 2013, DOJ had not launched any investigations or taken any enforcement actions based on the solicitations listed in the quarterly reports, because, according to DOJ officials, the reports have not indicated that any solicitation was unlawful.¹⁸ According to DOJ officials, based on information obtained separately from the quarterly reports, the agency has launched at least one investigation into activity in which there are indications of the illegal sales of shortage drugs through diversion.

FTC staff told us they investigate complaints about the gray market received from the public, as well as complaints referred to them by FDA and Congress, to determine whether an antitrust investigation is warranted. FTC receives complaints from the public through a toll-free telephone number, an email address, and through the U.S. mail.¹⁹ FTC staff told us that they review these complaints to determine whether there is enough information, such as evidence that the company is engaging in any coordinated antitrust behavior in violation of the Federal Trade Commission Act or the Clayton Act, to warrant an investigation. According to FTC staff, as of November 2013 they had not launched any full-phase investigations or taken any enforcement actions related to the pharmaceutical gray market. Though not a full-phase investigation, FTC staff told us that in the fall of 2011 they conducted an initial investigation to determine whether wholesale distributors or other parties were engaged in any conduct that violated federal antitrust laws, such as colluding to hoard drugs in shortage and then selling the drugs at higher

¹⁸In addition to their own review of gray market solicitations from FDA, DOJ officials told us that, at the request of FTC, DOJ could review complaints that suggest evidence of two or more actors engaged in criminal antitrust activity in violation of the Sherman Act. However, as of November 2013 DOJ had received no such referrals from FTC.

¹⁹Telephone complaints are received through 1-877-FTC-HELP. Email complaints are received through antitrust@ftc.gov.

prices. However, they were unable to find any evidence that widespread hoarding was occurring. Instead, they found cases where a single wholesale distributor acting alone would buy a few vials of a shortage drug and then sell it at a higher price—a practice that is not illegal.

In addition, in response to the Executive Order, federal agencies have worked together in an attempt to respond to gray market activities. In 2012, FDA, DOJ, FTC, and the National Association of Attorneys General convened three meetings to discuss the legal authorities that might apply to the gray market and the activities that each was undertaking related to this issue. Officials told us that in the future, they will meet on an “as needed” basis.

FDA officials told us that the agency is considering whether additional legal authorities to help address the pharmaceutical gray market and secure the drug supply chain would be beneficial. Such authorities may include registration and reporting requirements for wholesale distributors, potential prohibitions on wholesale distributors purchasing products from pharmacies, and pedigree and track-and-trace options.²⁰ FDA officials also noted that gray markets do not cause shortages, but are a symptom of such shortages. To the extent that FDA and other stakeholders address drug shortages, opportunities for gray markets to develop will become more limited. DOJ officials told us that DOJ does not have the authority to address drug pricing and stockpiling of drugs per se, but noted that the agency does have the authority to prosecute suppliers operating outside of the legal distribution system, regardless of the drug’s shortage status or price. Officials did not take a position as to whether additional authority over drug stockpiling and exorbitant pricing is necessary. FTC staff told us that they do not believe additional FTC

²⁰“Track-and-trace” refers to a system that involves electronically tagging each package with a unique identifier, noting each transfer of a drug package, and maintaining a database of all such transactions. During the course of our work, Congress enacted, and the President signed into law, the Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (2013). Among other things, the law requires wholesale distributors to report to FDA the states in which they are licensed and the status of those licenses. While not a registration requirement, FDA officials told us that this reporting requirement would provide the agency with the ability to identify the wholesale distributors in the marketplace. The law also requires manufacturers, wholesalers, and other drug supply chain participants to provide certain information and representations about pharmaceutical transactions when there is a change of ownership or possession of a drug product and requires the establishment of a national interoperable, electronic system to track certain prescription drugs through the supply chain.

authority in relation to the pharmaceutical gray market is necessary. They stated that the FTC's existing enforcement authority would be adequate to take action in relation to the inflated pricing of a shortage drug if such pricing was a consequence of anticompetitive conduct. If, however, the inflated pricing resulted from factors other than anticompetitive conduct, assessment of such issues would be outside the scope of the FTC's competition expertise.

Appendix IV: Summary of Recently Proposed Incentives to Alleviate or Prevent Drug Shortages

Some have suggested that incentivizing drug manufacturers to address the purported causes of drug shortages could alleviate or prevent such shortages. Proposed incentives include those related to regulatory activities undertaken by FDA or financial incentives that the federal government could provide to manufacturers.¹ Some incentives target immediate causes of drug shortages, such as by rewarding manufacturers for a strong quality record, thereby reducing the likelihood of quality-related supply disruptions, or by increasing redundancy in drug supply chains. Other proposed incentives target underlying causes, such as by increasing manufacturer revenue in order to encourage manufacturers to remain in the market and continue investments in production facilities.

This appendix provides a synopsis of incentives we identified that were (1) proposed by drug manufacturers and associations representing them in response to a February 2013 request from FDA for comment² or (2) included in bills introduced in the 112th Congress and 113th Congress, through June 2013.³ We reviewed all manufacturer and association responses to FDA's request for comment and identified 10 responses that included incentives to alleviate or prevent shortages. We identified one bill with provisions intended to create incentives to alleviate or prevent drug shortages.⁴ Next, we summarized the proposed incentives identified in our review and provided the summary list to

¹While this appendix focuses on incentives that could be offered by federal agencies, in its drug shortages strategic plan, FDA notes that the agency's ability to offer financial or other economic incentives is limited. FDA suggests that other stakeholders might explore economic, financial, or other means to incentivize innovation and new investments in manufacturing quality drugs to reduce the occurrence and severity of shortages.

²In February 2013, FDA published a notice in the Federal Register with a request for comment about its drug shortages task force and strategic plan. Two of FDA's questions related to incentives: *1c. Are there incentives that FDA can provide to encourage manufacturers to establish and maintain high-quality manufacturing practices, to develop redundancy in manufacturing operations, to expand capacity, and/or to create other conditions to prevent or mitigate shortages?* and *2. In our work to prevent shortages of drugs and biological products, FDA regularly engages with other U.S. Government Agencies. Are there incentives these Agencies can provide, separately or in partnership with FDA, to prevent shortages?* 78 Fed. Reg. 9928 (Feb. 12, 2013).

³The 112th Congress was in session from January 2011 to January 2013. The 113th Congress began in January 2013.

⁴The Patient Access to Drugs in Shortage Act of 2012 (H.R. 6611), introduced in the 112th Congress, was not enacted.

manufacturer and association representatives and to FDA for comment. We obtained comments from three leading national associations representing drug manufacturers, both brand and generic, and five generic sterile injectable manufacturers. For one incentive related to exempting certain products from Medicaid rebates and 340B discounts, we also obtained comments from relevant stakeholder groups whose members would be affected by this exemption.⁵

Regulatory Incentives

Expedited and streamlined reviews: Most of the comments submitted by manufacturers in response to FDA's request for comment proposed expediting or streamlining FDA review of regulatory submissions. Submissions that could be expedited included application supplements related to the approval of redundant manufacturing sites or new drug applications (NDA) or abbreviated new drug applications (ANDA) from manufacturers with a record of quality manufacturing and an adequate risk management plan to prevent shortages.⁶ According to FDA, as of June 30, 2013, there were more than 900 manufacturing supplements to NDAs, more than 5,700 manufacturing and chemistry supplements to ANDAs, and more than 2,700 ANDAs pending review. Therefore, proponents of expediting FDA review of regulatory submissions—including applications and supplements—note that increasing the speed of such reviews could provide an incentive to manufacturers to establish redundant manufacturing capacity to which production could be shifted in the event of manufacturing problems at a primary production facility, thereby avoiding a shortage. Further, by rewarding manufacturers with a history of quality manufacturing, expediting reviews could provide an

⁵Manufacturers who want to have their drugs covered by Medicaid on an outpatient basis must provide rebates to state Medicaid programs. These rebates offset the amount of the federal government's contribution to state Medicaid programs for expenditures for such outpatient drugs. Such manufacturers must also provide discounts to certain types of providers within the safety net through the 340B Drug Pricing Program.

⁶To receive approval to market a prescription drug in the United States, a manufacturer must submit an application to FDA demonstrating the drug's safety and effectiveness, describing the drug's manufacture, and providing information on the drug's labeling. FDA officials review such applications—including NDAs and ANDAs—and, where appropriate, inspect the establishments where the product will be manufactured. Once an application is approved, a manufacturer must notify FDA—through a supplement to said application or other regulatory submission—of any changes to that application, some of which require FDA's approval before the drug manufactured using the changed process can be distributed.

incentive to ensure quality-related production problems—and ensuing shortages—do not occur in the first place.

While representatives of the stakeholders we interviewed were generally supportive of this potential incentive, they also identified some limitations. One stakeholder cautioned that the resource-intensive nature of building in redundancy means it is a long-term solution, the implementation of which could hinder efforts to address current shortages. Another stakeholder noted that maintaining redundant manufacturing capacity is expensive and that expedited review alone may not provide enough of an incentive to establish such capacity. FDA officials noted that expediting reviews of regulatory submissions is a tool the agency already uses to address shortages. However, FDA officials cautioned that expanding the pool of submissions eligible for expedited review, without regard to the risk of shortage, could slow down review of all submissions and make expediting reviews meaningless. Representatives from one stakeholder echoed this concern, noting that, though faster than standard review times, in their experience there is already a backlog for review of supplements that have been expedited to address current shortages. Representatives from this stakeholder noted that without additional FDA resources devoted to the review of applications and supplements, making additional regulatory submissions eligible for expedited review would be problematic. FDA officials also noted that, although redundancy can help prevent a shortage if production stops, many shortages are the result of production disruptions driven by failures in manufacturing quality systems. Therefore, FDA officials told us that it is more important to prioritize incentives to improve manufacturing quality systems over those that expand capacity. To that end, as part of its drug shortages strategic plan goal to develop long-term prevention strategies in order to prevent shortages, FDA states that it will continue to expedite reviews to mitigate shortages, including the review of submissions for facility upgrades to improve quality.

Flexibility in meeting regulatory requirements: A few manufacturers proposed that FDA could allow for flexibility in meeting regulatory requirements for manufacturers with a strong history of compliance with current good manufacturing practice regulations or robust risk management plans to prevent shortages.⁷ For example, they suggest that

⁷Current good manufacturing practice regulations provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210, 211.

FDA could reduce the level of agency review for such change notifications as manufacturing site transfers, if the manufacturer had a history of production without quality issues.⁸ When proposing such incentives, supporters commented that, as it could allow manufacturers to implement manufacturing changes more quickly, reducing the level of agency review could provide an incentive for quality production. Incentivizing quality production could thus reduce the likelihood of a quality-related supply disruption and shortage. One stakeholder generally supported this approach, as long as all manufacturers were still held to the same standards and any change in requirements was accompanied by FDA guidance on the new approach. FDA officials told us that the agency has issued guidance documents to help identify types of changes after an application is approved that represent a lower risk. They added that the agency is currently exploring new approaches to the review of application products.

Decreased inspection frequency: Some manufacturers proposed the incentive of reduced frequency of FDA inspection for manufacturing establishments with a strong history of compliance with good manufacturing practices or robust risk management plans to prevent shortages.⁹ Proponents of such an approach told us that inspections are costly for the inspected establishment in terms of resources required to

⁸FDA guidance outlines reporting categories that govern the type of notification and FDA review required for various changes made after an application is approved, based on the potential of the change to adversely affect the safety or effectiveness of the drug. A change that has a substantial potential to adversely affect factors such as the identity, strength, quality, purity, or potency of a drug product require FDA review and approval of a “prior approval” supplement before a drug manufactured using this change can be distributed. For certain changes that may have a moderate potential to affect such factors, FDA may allow distribution of the drug 30 days after receipt of a “changes being effected” supplement, regardless of whether FDA has reviewed the changes. In some cases, FDA may allow distribution of the drug upon receipt of such supplement.

⁹To ensure that drugs are produced in conformance with federal statutes and regulations, including good manufacturing practice regulations, FDA may inspect the establishments where drugs are manufactured. We previously reported that FDA inspected domestic drug manufacturing establishments about once every 2.5 years and generally inspected foreign manufacturing establishments much less frequently. In part, this difference in frequency of inspection was due to the fact that, at the time, FDA was required to inspect every 2 years those domestic establishments that manufacture drugs in the United States, but there was no comparable requirement for inspecting foreign establishments. *GAO, Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress is Needed*, [GAO-10-961](#) (Washington, D.C.: Sept. 30, 2010).

respond to issues raised by the FDA investigator conducting the inspection and in terms of production disruptions caused by the inspection itself. As it could reduce costs and disruptions for the manufacturer, if carefully designed so that manufacturers would still be inspected with some frequency, increasing the interval between inspections may provide an additional incentive for compliance with good manufacturing practices, which could reduce the likelihood of manufacturing quality issues and resultant shortages. One stakeholder commented that decreasing inspection frequency could be an effective incentive in the long term, but at present, frequent inspections set a high bar for manufacturers in this industry. FDA officials noted that the agency already considers compliance history as a major factor when determining the frequency of inspection of a manufacturing site. Further, in response to new Food and Drug Administration Safety and Innovation Act (FDASIA) authority, the agency is in the process of establishing a risk-based inspection schedule for all establishments.¹⁰ FDA officials told us that they are considering incorporating additional factors, such as process performance metrics and shortage performance, into their selection model.

Transparency regarding compliance status of manufacturing sites: In documents submitted in response to FDA's request for comment, a few manufacturers proposed increasing the transparency of manufacturing establishment compliance status such as by assigning site scores or an FDA stamp of approval, which could help those engaged in drug purchasing and drug pricing negotiations—including providers, group purchasing organizations, insurers, and consumers—make informed purchasing and pricing decisions. Proponents of this approach suggest that FDA's provision of such quality metrics could make additional information publicly available for consideration in making purchasing and pricing decisions, thereby giving manufacturers an additional incentive for the highest quality production and making quality-related supply disruptions less likely to occur.

Representatives from the stakeholders we spoke with were generally skeptical of this approach. One noted that providers and group

¹⁰FDASIA removed the every-2-year domestic inspection requirement and instead requires FDA to determine the frequency of inspection for both domestic and foreign establishments on a risk-based schedule. Pub. L. No. 112-144 § 705, 126 Stat. 993, 1066 (2012).

purchasing organizations—which are the primary decision makers for sterile injectable purchases, where shortages have recently been concentrated—assume that quality is built in to any FDA-approved drug and may not be able to readily interpret quality metrics. Representatives from one stakeholder told us that FDA has spent extensive time and effort educating prescribers and the public that there is one quality standard for all FDA-approved drugs and that, from this stakeholder’s perspective, further differentiating quality with ratings would diminish confidence in the nation’s drug supply and lead to confusion and mistrust. Representatives from another stakeholder expressed skepticism that the market would respond to such information by allowing for higher prices. Likewise, representatives from multiple stakeholders noted that information about FDA inspections of manufacturing establishments and warning letters are already available online and are presumably already used when making purchasing and pricing decisions.

FDA officials confirmed that they currently provide information on the compliance status of manufacturing sites on the agency’s website and added that they are looking for new ways to provide transparency in this area.¹¹ They cautioned that there are significant questions and issues regarding how to provide more transparent compliance information to the public, such as the fact that FDA cannot disclose either confidential commercial information or trade secret information. Nevertheless, as part of its drug shortages strategic plan goal to develop long-term strategies in order to prevent shortages, FDA states that it is examining the broader use of quality metrics to assist in the evaluation of manufacturing quality. However, the plan also notes that although FDA can make quality information available to the public, including inspection outcomes, recalls, and shortages, buyers ultimately decide whether they will use these data when making purchasing decisions.

Financial Incentives

Guaranteed purchase: A few manufacturers proposed that the federal government guarantee the purchase of a given volume of certain drugs. This would allow manufacturers to ensure capacity for a given production volume regardless of whether there is sufficient market demand. Representatives from one stakeholder that supported this proposal told

¹¹<http://www.fda.gov/iceci/enforcementactions/ucm222557.htm>. Accessed December 3, 2013.

us that such an incentive might bring more predictability to both the volume of product made and product margins. In turn, this guarantee could create some predictability in a manufacturer's ability to invest in their facilities, resulting in continued high quality and compliant production. One stakeholder noted that such an incentive may be useful in terms of ensuring the availability of future capacity, but at present would not be an effective tool to address shortages as there is simply no excess capacity available even if the government could guarantee purchase volume. FDA officials noted that establishing such a program would be challenging. For example, identifying a list of drugs eligible for guaranteed purchase would be difficult, because it is hard to predict which drugs are vulnerable to shortage in advance and the particular drugs at risk of shortage may change rapidly.

Reduction in fees: Both recently-introduced federal legislation and some manufacturers proposed reducing manufacturer fees to help alleviate or prevent drug shortages. As introduced in the 112th Congress, H.R. 6611 proposed exempting certain drugs from the annual branded prescription drug fee established by the Patient Protection and Affordable Care Act in order to provide an incentive for brand-name drug manufacturers to enter the market to produce a drug in short supply.¹² Proponents of this approach state that a reduction in the annual branded prescription drug fee could induce brand-name companies to re-enter the market. One stakeholder also noted that brand-name manufacturers may have more idle capacity than generic manufacturers, so encouraging them to re-enter a market could be effective in addressing shortages.

A few manufacturers proposed a reduction in or waiver of various user fees if the manufacturer demonstrates that they have built redundant

¹²The annual fee is assessed according to each manufacturer's share of branded prescription drug sales to certain government programs, including Medicare and Medicaid. Pub. L. No. 111-148, § 9008, 124 Stat. 199, 859 (2010), as amended by Pub. L. No. 111-152, § 1404, 124 Stat. 1029, 1064 (2010). H.R. 6611—as introduced in the 112th Congress, but not enacted—would exclude the sales of any branded prescription drug, if in shortage, from the annual branded prescription drug fee.

capacity into their manufacturing plan.¹³ Proponents of user fee reductions noted that building redundancy into a manufacturing plan is resource intensive and that a fee reduction to help offset these costs could incentivize manufacturers to build redundancy which could help prevent supply disruptions. At the same time, one stakeholder that supported this approach noted that, though user fees add up, reducing such fees would not make a large enough economic difference to impact a manufacturer's decision to enter or exit a market. FDA officials first noted that any changes to the user fee structure would have to be negotiated with industry and then enacted by Congress. They stated that, although the agency is open to using user fees as a way to prevent shortages and encourage manufacturers to help address a shortage that does arise, there are some uncertainties about doing this. For example, definitions of redundancy are unclear and mechanisms ensuring redundant capacity is not repurposed would need to be developed and enforced. Finally, FDA officials also cautioned that reducing or waiving fees for certain manufacturers could increase fees on other manufacturers. This is because the total amount of user fees FDA collects is fixed in statute and the annual fees assessed against individual manufacturers are determined by dividing the fixed statutory amount by the forecasted number of fee-paying entities. As a result, elimination of, or a reduction in, fees for some parties would effectively transfer these costs to the remaining fee-paying entities.

Tax incentives: In order to offset the costs of such investment, some manufacturers proposed tax credits targeted to manufacturers that invest in redundant manufacturing capacity. Multiple stakeholders noted that, given the significant costs associated with new manufacturing establishments, such an incentive would only be effective for manufacturers that already operated such establishments. Representatives from one stakeholder noted that the time, resources, and

¹³Federal law requires FDA to collect various fees, known as "user fees," from brand-name human drug and biological product manufacturers to supplement the cost of reviewing new drug applications and inspecting establishments. 21 U.S.C. § 379h. One manufacturer comment proposed reducing or waiving the establishment fee for manufacturers that built in redundant manufacturing capacity. For fiscal year 2013, the establishment fee for new drugs was \$526,500 per establishment. Federal law also directs FDA to collect similar user fees from generic manufacturers. 21 U.S.C. § 379j-42. Two manufacturer comments proposed offsetting filing fees for manufacturers that built redundancy into their manufacturing plan. For fiscal year 2013, the application fee for a generic drug application is \$51,520.

approvals to create a new manufacturing site are likely to take more than 3 years with associated costs totaling tens of millions of dollars. Therefore, tax credits are a strong incentive for companies to re-invest in existing infrastructure, not necessarily to create new infrastructure. FDA officials told us that modernizing existing facilities to prevent quality and safety issues that lead to shortages can go a long way to prevent shortages even in a system with little redundancy. They noted that such incentives would need to encourage manufacturers to purchase new equipment, renovate facilities, and implement new manufacturing processes and technologies.

Changes in drug pricing or reimbursement: As introduced in the 112th Congress, H.R. 6611 proposed changing the reimbursement rate or pricing system for generic sterile injectable products for which there are three or fewer active manufacturers. Such changes are intended to prevent shortages by providing an incentive to manufacturers to continue production in a concentrated market. Specifically, the bill proposed changing the calculation of the Medicare reimbursement rate for generic sterile injectable products for which there are three or fewer active manufacturers from average sales price plus 6 percent to wholesale acquisition cost.¹⁴ It would also exempt such products from Medicaid rebates and 340B discounts.

The premise of the Medicare reimbursement change proposal is that basing reimbursement on wholesale acquisition cost will enable manufacturers to adjust their prices to meet supply and demand, which

¹⁴Average sales price is the weighted average of all non-federal U.S. sales by manufacturers net of chargebacks, discounts, rebates, and other price concessions tied to the purchase of the drug product, whether it is paid to the wholesale distributor or the entity that purchases the drug. Wholesale acquisition cost is the manufacturer's list price for the drug product to wholesalers or direct purchasers not including any discounts, rebates, or reductions in price.

some claim the current reimbursement structure prevents.¹⁵ By allowing manufacturers to more readily adjust their prices and achieve a profit, this proposal aims to provide an incentive for manufacturers to remain in the market, thereby preventing further erosion of manufacturing capacity, which could make the generic sterile injectable market even more vulnerable to shortages. Proponents note that this incentive could positively affect manufacturer profit and influence a manufacturer's decision about participating in the market for a particular drug. One stakeholder cautioned that, in their opinion, using reimbursement as an incentive increases the risk of fraud and abuse.

The premise of the Medicaid rebate and 340B discount exemptions proposal is that such rebates exert additional downward pressure on already extremely low prices, thereby limiting manufacturers' ability to sustain production and upgrade facilities. Removing such rebates and discounts would provide additional revenue to manufacturers, thereby potentially providing them an incentive to remain in the market and maintain manufacturing capacity or to re-enter the market. Proponents state that this incentive may help influence manufacturer margins, thereby providing revenue to invest in production capacity to ensure demand is met. However, some stakeholders caution that these exemptions would increase costs to patients and the government (including increasing drug costs and administrative costs to the government for tracking such an exemption). Representatives from one stakeholder group we interviewed noted that, according to its inquiries, the majority of generic sterile injectable drugs are manufactured by three or fewer manufacturers, in which case nearly all such drugs would be subject to this exemption, whether the drug had ever been in shortage or not. Further, stakeholders

¹⁵To calculate the average sales price, manufacturers submit sales data to the Centers for Medicare & Medicaid Services within 30 days of the end of each quarter. The agency then uses that data to set reimbursement rates for the following quarter. For example, manufacturers submitted sales data for the quarter covering October to December 2012 to the Centers for Medicare & Medicaid Services in January 2013 and the agency used those data to set reimbursement rates effective in April 2013. Therefore, some commentators have claimed that this two quarter lag limits manufacturers' ability to adjust prices. For example, if a manufacturer changes the price of a drug in October 2012, the reimbursement to providers will not change until April 2013 (two quarters later), potentially creating a disincentive to purchase these drugs if the reimbursement is less than the purchase price for this period. Others note that manufacturers can and do adjust their prices and note that under the current reimbursement system, when the price of a drug drops, such as when a drug goes off patent, providers are reimbursed for more than the purchase price for the period until the reimbursement catches up.

noted that generic sterile injectable drugs are often administered in hospital inpatient departments and are therefore not subject to Medicaid rebates, which only apply to outpatient drugs. One stakeholder stated that for the few drugs in this group that are subject to Medicaid rebates, the cost of these drugs is already low, which would result in a minimal financial impact of such an exemption. Finally, one stakeholder stated that 340B discount exemptions would have a minimal influence on drug shortages.

Appendix V: 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

JAN 17 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, "Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability" (GAO-14-194).

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

**THE DEPARTMENT OF HEALTH AND HUMAN SERVICES' (HHS)
GENERAL COMMENTS TO THE GOVERNMENT ACCOUNTABILITY
OFFICE'S DRAFT REPORT, ENTITLED, "DRUG SHORTAGES: PUBLIC
HEALTH THREAT CONTINUES, DESPITE EFFORTS TO HELP ENSURE
PRODUCT AVAILABILITY" (GAO-14-194)**

HHS is committed to the prevention of new drug shortages and the resolution of ongoing drug shortages, which remain a significant public health issue in the United States. The GAO report recognizes HHS's successes in preventing and mitigating drug shortages. As the GAO report notes, we have done this by making the best use of the increase in notifications from manufacturers and other stakeholders since the President issued his Executive Order and Congress enacted the FDA Safety and Innovation Act (FDASIA). HHS will continue to use every tool available under its existing authorities to respond to potential shortage threats.

We agree that, while HHS has made considerable progress in preventing new shortages, some shortages persist. However, we are concerned that the data presented by GAO may overstate this problem by counting any shortage where not all National Drug Codes have been restored by all manufacturers as an ongoing shortage. This overstates shortage persistence because there are many instances where not all manufacturers are producing all product codes but the manufacturers that are currently producing the drug have increased production of their product codes to meet all demand.

HHS agrees with the GAO recommendations to continue improving the collection of drug shortage data and to better leverage such data, where possible, to assist in identifying trends, clarifying causes, and resolving problems before drugs go into short supply. HHS considers the drug shortage data as one part of a larger system of data that would help identify problems with quality drug manufacturing as they evolve. The focus of this effort is on preventing shortages by getting ahead of quality problems, consistent with the long-term approach laid out in FDA's October 2013 Strategic Plan for Preventing and Mitigating Drug Shortages (Drug Shortage Strategic Plan).
<http://www.fda.gov/downloads/drugs/drugsafety/drugshortages/ucm372566.pdf>

HHS agrees that there are many factors that can trigger or exacerbate a shortage; however, we lack the relevant data to create a comprehensive forecasting system for drug shortages. For example, we do not have access to economic/product margin information or detailed data associated with manufacturing capability or capacity. A comprehensive forecasting system would require this information both for drugs in shortage and not in shortage.

HHS agrees that policies and procedures for data entry are important to help assure the timely, accurate, and consistent inputting of data into the drug shortage database. As GAO points out, FDA has ongoing work that is summarized in the FDA's Drug Shortage Strategic Plan to assure that such policies and procedures are established. HHS will also continue its dialogue with manufacturers and other stakeholders to help ensure that drugs are available to patients who need them.

Appendix VI: GAO Contact and Staff Acknowledgments

GAO Contact

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

Staff Acknowledgments

In addition to the contact named above, Geri Redican-Bigott, Assistant Director; Katherine L. Amoroso; Zhi Boon; Leia Dickerson; Sandra George; Alison Goetsch; Cathleen Hamann; Rebecca Hendrickson; Eagan Kemp; Sarah-Lynn McGrath; Yesook Merrill; and Leslie Powell made key contributions to this report.

Related GAO Products

Drug Compounding: Clear Authority and More Reliable Data Needed to Strengthen FDA Oversight. [GAO-13-702](#). Washington, D.C.: July 31, 2013.

High-Risk Series: An Update. [GAO-13-283](#). Washington, D.C.: February 2013.

Drug Shortages: FDA's Ability to Respond Should Be Strengthened. [GAO-12-315T](#). Washington, D.C.: December 15, 2011.

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