United States Government Accountability Office

Report to Congressional Committees

July 2016

# DRUG SHORTAGES

# Certain Factors Are Strongly Associated with This Persistent Public Health Challenge

GAO-16-595

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## Certain Factors Are Strongly Associated with This Persistent Public Health Challenge

GAO Highlights

Highlights of GAO-16-595, a report to congressional committees

## Why GAO Did This Study

Drug shortages are a serious public health concern. GAO previously found that many shortages were of sterile injectable drugs and could generally be traced to supply disruptions caused by manufacturers slowing or halting production to address quality issues.

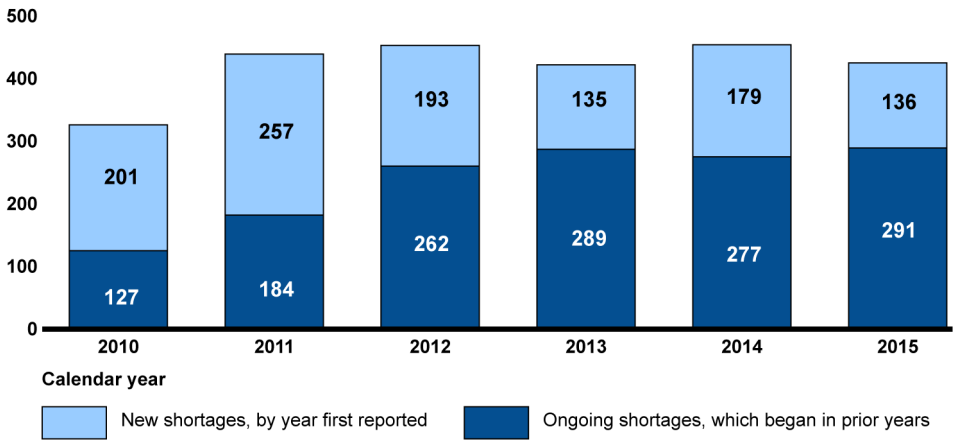
Congress included a provision in statute for GAO to review several aspects of drug shortages. This report examines (1) trends in drug shortages, (2) FDA's efforts to prioritize reviews of drug submissions to address shortages, (3) trends in FDA warning letters issued to sterile injectable manufacturing establishments for noncompliance with manufacturing standards, and (4) the relationship between certain factors and shortages of sterile injectable drugs. GAO analyzed—using various methods including regression analyses—drug shortage data from the University of Utah Drug Information Service from 2010 through 2015; drug sales data from IMS Health from 2010 through 2014 for sterile injectable anti-infective and cardiovascular drugs (which have been subject to multiple and prolonged shortages); and FDA data, including data on warning letters related to inspections conducted from October 2006 through September 2013 and data on prioritized reviews from January 2010 through July 2014, which were generally the latest available data at the time GAO began its analysis. GAO also interviewed FDA officials and reviewed agency documents, including documents related to the issuance of warning letters to seven establishments FDA and others said were linked to widespread shortages.

View GAO-16-595. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

## What GAO Found

When available supplies of prescription drugs are insufficient, patient care may be adversely affected. The number of new shortages has generally decreased since 2011, while the number of ongoing shortages remained high.

**Number of Drug Shortages from January 2010 through December 2015**




Source: GAO analysis of University of Utah Drug Information Service data. | GAO-16-595

To help address shortages, the Food and Drug Administration (FDA) prioritized the review of—more quickly reviewed—383 drug applications and supplements during the time period GAO examined. Most were for generic sterile injectable drugs. FDA's approval of some of these submissions occurred before the shortage was resolved. Although the timing of FDA's approval does not establish a causal link, it could indicate that FDA's action helped address some shortages.

GAO found that, as part of FDA's oversight of drug safety and quality, it generally issued an increasing number of warning letters to sterile injectable drug establishments during the time period GAO reviewed for noncompliance with manufacturing standards outlined in federal regulations. However, the percentage of inspections resulting in warning letters remained relatively small as the number of inspections also increased. Moreover, seven establishments that were linked to widespread shortages and received warning letters all had previous indications of difficulty complying with manufacturing standards.

Shortages of sterile injectable anti-infective and cardiovascular drugs in 2012, 2013, and 2014 were strongly associated with certain factors GAO examined. Two factors—a decline in the number of suppliers and failure of at least one establishment making a drug to comply with manufacturing standards resulting in a warning letter—suggest that shortages may be triggered by supply disruptions. A third factor—drugs with sales of a generic version—suggests that due to relatively low profit margins for generic drugs, manufacturers are less likely to increase production, making the market vulnerable to shortages. The Department of Health and Human Services (HHS) reviewed a draft of this report and reiterated its commitment to addressing drug shortages. GAO incorporated HHS's technical comments as appropriate.

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**Abbreviations**

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|---|---|
| ANDA | abbreviated new drug application |
| ASHP | American Society of Health-System Pharmacists |
| DSS | Drug Shortage Staff |
| FDA | Food and Drug Administration |
| HHS | Department of Health and Human Services |
| NDA | new drug application |
| UUDIS | University of Utah Drug Information Service |

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July 7, 2016

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

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

Shortages of prescription drugs continue to be a serious public health concern. When available drug supplies are insufficient to meet medical needs, patient care may be adversely affected. Drugs in shortage include those that are essential therapies, such as antibiotics, chemotherapy agents, cardiovascular drugs, and pain medications. Shortages can result in delayed patient care and medication errors. They may also result in rationing, which can lead to the use of less effective treatments and force providers to make difficult choices, such as deciding which cancer patients should start or complete a round of chemotherapy. In light of the effect such shortages can have on public health, the Food and Drug Administration (FDA) works within the scope of its authority to ensure drug availability by taking actions to address—prevent, mitigate, or resolve—drug shortages.[1]

We previously found that many shortages were of sterile injectable drugs and that their immediate cause could generally be traced to supply disruptions triggered by a manufacturer slowing or halting production to

[1]FDA is an agency within the Department of Health and Human Services, and it is responsible for overseeing the safety and effectiveness of drugs marketed in the United States and protecting public health.

address quality problems.[2] In addition to this immediate cause, for our 2014 report, we conducted a literature review and from that we also identified potential underlying causes of shortages that were particular to the economics of the generic sterile injectable drug market, such as low profit margins limiting infrastructure investments or leading some manufacturers to exit the market. Also cited in the literature we reviewed as causes of shortages were more rigorous inspections of drug manufacturing establishments by FDA and an increase in warning letters issued by the agency.[3] Proponents of this view maintained that warning letters caused shortages as establishments slowed or shut down production in response to receiving the letters. Opponents of this view counter that manufacturers encountered quality problems resulting from noncompliance with manufacturing standards, which led to both the issuance of these letters and shortages.

To help address some shortages, regardless of the cause, FDA has stated in its drug shortages strategic plan that it prioritizes its review of submissions from drug sponsors seeking approval to bring a similar drug to market.[4] These submissions may include applications to market an additional generic version of a drug in shortage or supplemental applications, requests to make certain changes to already approved generic or brand-name drug applications. An example of a supplemental

[2]GAO, *Drug Shortages: FDA's Ability to Respond Should Be Strengthened*, GAO-12-116 (Washington, D.C.: Nov. 21, 2011) and *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability*, GAO-14-194 (Washington, D.C.: Feb. 10, 2014). For a list of these and other related reports, see the Related GAO Products at the end of this report.

[3]FDA issues warning letters when it identifies violations that, if not promptly and adequately corrected, may lead the agency to take enforcement actions, such as seeking court action to stop an establishment from manufacturing and distributing a product until the violation is corrected.

[4]See Food and Drug Administration, *Strategic Plan for Preventing and Mitigating Drug Shortages* (October 2013). When an application or supplement is prioritized, it is considered more quickly by FDA review staff than it otherwise would be and therefore rises up in a reviewer's queue of submissions.

application requiring FDA approval would be one that adds a new manufacturing site.[5]

Congress included a provision in the Food and Drug Administration Safety and Innovation Act for us to review several different aspects of drug shortages.[6] Our February 2014 report examined these issues, and this report continues to explore drug shortages and FDA's management of them in more detail. Specifically, this report examines

1. trends in recent drug shortages;
2. FDA's prioritization of reviews of drug submissions to address drug shortages;
3. trends in FDA warning letters issued to sterile injectable drug manufacturing establishments for noncompliance with manufacturing standards; and
4. the relationship between certain factors and shortages in the sterile injectable drug market.

To examine trends in recent drug shortages, we analyzed data from the University of Utah Drug Information Service (UUDIS) to identify drugs that were in short supply from January 2010 through December 2015, which were the most recent data available at the time we conducted our work.[7] These data are generally regarded as the most comprehensive and reliable source of drug shortage information for the time period we reviewed. Although UUDIS and FDA both track and maintain information about drug shortages, we used the data maintained by UUDIS because

[5]FDA's review and approval of an application is required before a drug can be marketed for sale in the United States. In addition, FDA review and approval is required for certain changes to the original application—such as changes to the product manufacturing location or process, type or source of active ingredients, or the product's labeling—if the change has a substantial potential to adversely affect the drug product's identity, strength, quality, purity, or potency. We use the term "submission" to refer to both applications and supplemental applications submitted to FDA.

[6]Pub. L. No. 112-144, § 1008, 126 Stat. 993, 1107 (2012).

[7]Our analysis focuses on shortages of prescription drugs, so we excluded shortages of over-the-counter drugs, biologics (including vaccines), medical devices, and orally-administered vitamins from our analysis even though UUDIS also tracks and includes these shortages in its data. 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.

part of the time period we reviewed predates FDA's establishment of a data tracking system. (See app. I for a comparison of FDA and UUDIS drug shortage data.) UUDIS's data are also what we used in preparing our 2011 and 2014 reports on drug shortages.[8] 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. We also obtained information from representatives of the 10 national associations representing health care providers, including physicians and pharmacists that we interviewed for our 2014 report regarding their experiences with drug shortages in recent years.[9] We asked them to respond to open-ended questions and did not independently validate their responses.

To examine FDA's prioritization of reviews of drug submissions to address drug shortages, we analyzed data from FDA's Document Archiving, Reporting, and Regulatory Tracking System on all submissions—drug applications and drug application supplements—for which FDA prioritized its review to address drug shortages. Specifically, we analyzed all the submissions that FDA received and prioritized for this reason from January 2010 through July 2014, the most recent data available when we began our analysis. In response to a shortage or potential shortage of one drug, FDA can prioritize more than one submission. To examine FDA's prioritization process in greater detail, we selected a subset of the prioritized submissions. To select this subset, we first identified all submissions for which FDA prioritized its review during a shorter time period—January 2013 through June 2013.[10] As we used the drug as the unit of analysis, we next identified the number of drugs associated with those prioritized submissions.[11] The submissions that FDA prioritized for review during this shorter time period were associated with 38 drugs. Finally, as FDA may have prioritized its review of other submissions related to these 38 drugs outside of this short time frame, we

[8]See GAO-12-116, 2, and GAO-14-194, 2.

[9]See GAO-14-194, 64.

[10]We focused on this shorter time period as the initial step for selecting the subset because it would allow for a reasonably sufficient amount of time to elapse for FDA to have completed its review of these submissions and for the shortages associated with them to have been prevented or resolved.

[11]For the purposes of our analysis, we consider a drug to be a unique combination of active ingredient and dosage form (e.g., acyclovir sodium injection).

identified any additional submissions for these drugs for which FDA prioritized its review from January 2010 through July 2014. In total, the 38 drugs were associated with 153 prioritized submissions. We compared the data on these prioritized submissions to FDA's drug shortage data, which include information on actual shortages and shortages FDA classifies as prevented, to determine whether at least one submission for each drug may have contributed to the prevention or resolution of a shortage of the drug. For the purposes of this analysis, we determined that a submission may have contributed to the prevention or resolution of a shortage if it was approved before the shortage of that drug was prevented or resolved. The status of each submission—such as whether FDA had approved it or whether it was still under review at FDA—was as of October 30, 2014, the date FDA extracted the data.[12] To assess the reliability of FDA's prioritized review data and drug shortage data we reviewed related documentation, interviewed knowledgeable agency officials, and reviewed the data for missing information, discrepancies, or logical errors. We found these data sufficiently reliable for the purposes of our report. Lastly, we reviewed FDA guidance and policies regarding prioritized reviews and interviewed relevant FDA officials about the agency's approach to prioritizing reviews of submissions to address shortages.

To examine trends in FDA warning letters issued to sterile injectable drug establishments for noncompliance with manufacturing standards, we obtained 2009 and 2014 drug registration and listing data from FDA to identify all foreign and domestic establishments that were listed as

[12]The data we analyzed may understate the number of submissions that FDA prioritized prior to October 2013, because, according to FDA officials, reviewers were not required to record all types of submissions that had been prioritized to address shortages before that time. There also may have been submissions relevant to shortages that FDA did not prioritize, but the information obtained from FDA did not permit us to identify such instances.

manufacturing at least one sterile injectable product.[13] We also obtained inspection data from FDA's Field Accomplishments and Compliance Tracking System on drug manufacturing establishment inspections that were conducted from October 2006 through September 2013. Using the registration and listing data, we identified inspections of foreign and domestic establishments manufacturing sterile injectable drugs and non-injectable drugs.[14] We also obtained data on warning letters citing non-compliance with manufacturing standards that were issued to human drug manufacturing establishments following inspections conducted from October 2006 through September 2013. Using the registration and listing data, we identified warning letters issued to foreign and domestic establishments manufacturing sterile injectable drugs and non-injectable drugs.[15] To assess the reliability of FDA's drug registration and listing, inspection, and warning letter data, we reviewed related documentation, interviewed knowledgeable agency officials, and performed electronic data testing for missing information, outliers, or logical errors. For our

[13]Domestic and foreign establishments that manufacture drugs for the U.S. market are required to register annually with FDA and to provide a list of drugs they manufacture. 21 U.S.C. § 360(b), (i)(1), (j)(1). Our use of registration and listing data to identify sterile injectable drug manufacturing establishments may overstate the number of such establishments if (1) an establishment listed that it manufactured a sterile injectable drug for the U.S. market, but did not actually do so, or (2) an establishment discontinued the manufacture of its sterile injectable products, but did not report that to FDA as required, or (3) an establishment only manufactured a sterile injectable drug for part of our time frame, as we categorized an establishment as one marketing sterile injectable drugs if it was listed as the manufacturing location of at least one sterile injectable drug at any point during our time frame. At the same time, our use of these data may understate the number of such establishments if an establishment manufactured a sterile injectable drug for the U.S. market, but failed to register and list that drug. FDA officials were unable to quantify the extent to which registration and listing data may erroneously include or exclude sterile injectable drug manufacturing establishments.

[14]If an establishment was listed as the manufacturing location of at least one sterile injectable product, we classified that establishment as a sterile injectable establishment and inspections of that establishment as sterile injectable establishment inspections. However, establishments may manufacture multiple dosage forms, including sterile injectable drugs and non-injectable drugs, such as tablets or ointments. Therefore, our count of sterile injectable establishment inspections may be an overcount if FDA focused on the manufacture of non-injectable drugs during inspections of establishments manufacturing both dosage forms.

[15]As with our inspection data, if an establishment was listed as the manufacturing location of at least one sterile injectable product, we classified warning letters issued to that establishment as sterile injectable warning letters. Therefore, our count of sterile injectable warning letters may be an overcount if the violations listed in a warning letter were related to an establishment's non-injectable manufacturing processes only.

inspection and warning letter data we also compared our counts to published data and compared a selection of our warning letter data to source documents. We found all of these data sufficiently reliable for our purposes. We also analyzed UUDIS data on shortages of sterile injectable drugs from October 2006 to September 2013. In addition to analyzing these data, we interviewed FDA officials and reviewed FDA policies and procedures related to selecting establishments for inspection, conducting inspections, classifying the results of establishment inspections, and issuing warning letters. Finally, FDA and others have linked seven major sterile injectable manufacturing establishments to widespread shortages.[16] For this group of seven establishments, we examined materials related to the recommendation for, internal review of, and issuance of all warning and untitled letters associated with inspections of these establishments conducted from October 2006 through September 2013.[17]

To examine the relationship between certain factors and sterile injectable drug shortages, we used data from IMS Health to identify all sterile injectable anti-infective and cardiovascular drugs with sales—118 drugs total—from 2010 through 2014, the most recent data available when we began our analysis. We chose these two therapeutic classes of drugs because they both have been subject to multiple and prolonged shortages and prior studies have focused on other classes such as oncology.[18] We estimated a regression model using 3 years of shortage history for each drug in our study to examine the relationship between whether a drug was in shortage during 2012, 2013, or 2014 (dependent variable), and four factors (the explanatory variables). We based our dependent variable for drug shortages on UUDIS data. We classified a drug as being in shortage if it was in shortage any time during a given

[16]The seven establishments are Ben Venue Laboratories, Inc., establishment in Bedford, OH; Fresenius Kabi USA, LLC, establishment in Grand Island, NY; Hospira, Inc., establishments in Rocky Mount, NC, and Clayton, NC; Luitpold Pharmaceuticals, Inc., establishment in Shirley, NY; Sandoz Canada, Inc., establishment in Boucherville, Quebec, Canada; and Teva Parenteral Medicines, Inc., establishment in Irvine, CA.

[17]FDA issues untitled letters when serious violations of manufacturing standards are found, but the violations do not meet the threshold of regulatory significance for a warning letter.

[18]As part of our work we spoke to representatives of the American College of Cardiology and the Infectious Diseases Society of America who confirmed that shortages of these drugs have been consistently problematic in recent years.

calendar year, including shortages that started in a prior year and remained ongoing. We used IMS Health data to create three of the binary explanatory variables: sales of a generic version, a decline in the number of suppliers, and price decline.[19] We created the fourth binary explanatory variable, noncompliance with manufacturing standards by an establishment that resulted in the receipt of a warning letter, using FDA's drug registration and listing data and warning letter data. This is a unique explanatory variable that provides a direct measure of compliance with FDA's manufacturing standards. See appendix II for more on the data sources and methodology for this analysis. We took several steps to ensure that the data used to produce this analysis were sufficiently reliable. Specifically, we assessed the reliability of the IMS Health National Sales Perspectives™ data by interviewing officials at IMS Health. We also reviewed relevant documentation and examined the data for obvious errors, such as missing values and values outside of expected ranges.

Our analysis of the relationship between certain factors and drug shortages has some limitations. First, our findings are limited to data for sterile injectable anti-infective and cardiovascular drugs that were marketed and sold from 2010 through 2014 and shortages in these two therapeutic classes from 2012 through 2014. Our findings are not generalizable to drugs in other routes of administration, other therapeutic classes, or shortages during other time periods. Second, missing manufacturing location data may have caused us to underestimate or overestimate the relationship between shortages and noncompliance with manufacturing standards resulting in a warning letter. For the drugs in our study that were missing manufacturing location data, we could not always identify whether the drugs were manufactured by at least one establishment that received a warning letter. Therefore, we may have misclassified some drugs that were manufactured by establishments that received a warning letter as drugs manufactured by establishments that did not receive a warning letter. Whether we may have overestimated or underestimated the relationship depends on whether the potentially

[19]We use the term "supplier" to describe the company name on drug labels. The company whose name is on the drug label may or may not be the same as the manufacturer of the drug. A drug's supplier could be different from its manufacturer if the labeler is actually a repackager, a distributor, the parent company of the manufacturer, or if the supplier contracts with another manufacturer—known as a contract manufacturer—to produce the drug on the supplier's behalf.

misclassified drugs were in shortage. If these potentially misclassified drugs were in shortage, our model may underestimate the relationship between shortages and receipt of a warning letter. If these potentially misclassified drugs were not in shortage, our model may overestimate the relationship between shortages and receipt of a warning letter. The extent to which we may have underestimated or overestimated this relationship is unclear. For 57 of the 118 drugs in our study, we found partial manufacturing location data, and for 3 drugs we found no manufacturing location data. We were not able to identify these data for drugs if the IMS data did not include a national drug code for a particular product or if the manufacturer was not listed in FDA's drug registration and listing data.

We conducted this performance audit from June 2014 to July 2016 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

# Background

## FDA's Oversight of Drugs

FDA's approval is required before brand-name drugs and generic drugs can be marketed for sale in the United States.[20] To obtain FDA's approval to market a brand-name 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. To obtain FDA's approval to market a generic drug, sponsors must submit an abbreviated new drug application (ANDA). 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.[21] If a sponsor wants to change any part of its original NDA or ANDA after its approval—such as changes to manufacturing location or process, the type or source of active ingredients, or the labeling—it must generally submit an application supplement to notify FDA of the change. If

[20]21 U.S.C. § 355(a).

[21]21 U.S.C. § 355(j).

the change has a substantial potential to adversely affect factors such as the identity, strength, quality, purity, or potency of the drug, the sponsor must obtain FDA approval.[22] As part of the application and application supplement review process, FDA may conduct an inspection of the establishment where the drug will be manufactured to verify the accuracy and authenticity of the data contained in the application, to determine that the establishment is following commitments made in the application, and to verify that the establishment is prepared to make the drug named in the application or supplement.

After approving brand-name and generic drugs for marketing in the United States, FDA's oversight responsibilities continue, as it is charged with monitoring their safety, effectiveness, quality, and promotion. FDA periodically inspects drug manufacturing establishments, including those manufacturing brand-name, generic, and over-the-counter drugs to assess their ongoing compliance with current good manufacturing practice regulations.[23] In addition to these surveillance inspections, FDA may also conduct for-cause inspections when the agency receives information indicating problems in the manufacture of marketed drugs, among other reasons. FDA may conduct an inspection that includes multiple components (e.g., both preapproval and surveillance) during a single visit to an establishment. Based on the agency's findings during an inspection, FDA classifies the inspection as either (1) no action indicated, when insignificant or no deficiencies were identified; (2) voluntary action indicated, when deficiencies were identified and must be corrected, but the agency is not prepared to take regulatory action; or (3) official action indicated, when serious deficiencies were found that warrant regulatory action.

Specifically, if FDA identifies a violation of law or regulations during an inspection and therefore finds the establishment to be out of compliance with manufacturing standards, the agency may issue a warning letter. FDA issues warning letters when the agency has identified violations that may lead to enforcement action if not promptly and adequately corrected. Recommendations to issue a warning letter are either made by staff in FDA's district offices or by staff in FDA's Center for Drug Evaluation and

[22]21 C.F.R. §§ 314.70, 314.97 (2015).

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

Research. Multiple levels of the Center's staff review all warning letter recommendations. It is FDA policy to consider many factors in determining whether to issue a warning letter. For example, the agency is to consider the compliance history of the establishment, the nature of the violation (e.g., whether the establishment was aware of the violation, but failed to correct it), and the risk associated with the product and the impact of the violation on such risk. FDA is also to consider corrective actions taken or promised by the establishment since the inspection, and it may decide not to issue a letter if an establishment's corrective actions are adequate and the violations that would have supported the letter have been corrected. To determine whether actions planned or taken by an establishment to correct violations are adequate FDA may, among other activities, review documentation describing proposed or completed corrective actions or hold meetings with representatives of the establishment to discuss these actions. FDA is also required by law to consider whether issuing the warning letter could reasonably cause or exacerbate a shortage of a life-saving drug.[24] If it determines a shortage could occur or an existing shortage could worsen, 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 from not taking action. Once issued, warning letters are publicly posted on FDA's website.

## FDA Oversight of Drug Shortages

FDA's Drug Shortage Staff (DSS) coordinates the agency's response to drug shortages. FDA is notified of actual and potential drug shortages by manufacturers, health professionals, and the public.[25] Once DSS becomes aware of a potential or actual shortage, DSS attempts to determine whether the total supply of the drug and any pharmaceutical equivalents is inadequate to meet demand. To verify that a shortage is in effect or a potential shortage is pending, DSS contacts all manufacturers of the drug to collect up-to-date information on the inventory and demand

[24]21 U.S.C. § 356c(b)-(c). The law 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.

[25]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. 21 U.S.C. § 356c.

for the drug and manufacturing schedules. DSS also analyzes market research data from IMS Health to compare current supply of the drug with historical demand.

DSS coordinates as needed with several other FDA offices including the Office of Generic Drugs and the Office of Compliance to address drug shortages. Once DSS verifies a shortage or potential shortage of a drug, it may seek assistance from these offices to address that shortage, including the following:

- identifying the extent of the shortage and determining whether other manufacturers are willing and able to increase production of the shortage drug;
- prioritizing reviews of drug applications, supplements, and inspections for manufacturers attempting to restore, increase, or begin production of the shortage drug; and
- applying regulatory discretion, such as refraining from taking enforcement action to stop the distribution of a drug that is in shortage despite a labeling or quality issue.

For example, DSS provides the Office of Generic Drugs with drug shortage information so that the office can identify ANDAs or ANDA supplements it can prioritize its review of to address a shortage.

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. Finally, FDA cannot control the prices of marketed drugs.

## Characteristics of the Sterile Injectable Drug Industry

In our February 2014 report, we identified unique characteristics of the sterile injectable drug industry that may make these drugs susceptible to shortages.[26] These characteristics include limited inventory, need for regulatory approval, production complexity, and constrained manufacturing capacity.

[26]GAO-14-194.

- **Limited inventory.** The widespread use of "just-in-time" inventory practices can increase the vulnerability of the supply chain to shortages. For example, according to one manufacturer representative, 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, when a manufacturer stops production, a shortage can result quickly.

- **Regulatory approval**. New manufacturers may not be able to quickly enter the market to produce a drug in shortage because FDA's approval of an ANDA—which can take more than a year—is required. Further, even existing manufacturers of the drug need FDA approval of changes to manufacturing conditions or processes that have a substantial potential to adversely affect factors such as the identity, strength, quality, purity, or potency of the drug before the drug manufactured under the new conditions or processes can be marketed. For example, FDA approval of an application supplement may be required for changes in location of a manufacturing site or the source of the raw materials or components for manufacturing a drug.

- **Production complexity.** Costly, specialized equipment is required to manufacture prescription drugs and production processes are complex, particularly for sterile injectables.[27] Maintaining sterility throughout the production process is challenging, yet it is particularly important for these drugs as serious injury can occur if contaminated drugs are injected into patients. Some generic sterile injectable drugs need to be manufactured on lines or in facilities dedicated solely to those drugs, thus creating challenges for new manufacturers to enter the market. We previously found that sterile injectable anti-infective and oncology drugs require lines, and sometimes whole facilities, that are limited to the production of such drugs. For example, some anti-infective drugs, such as penicillin, can trigger serious allergic reactions at very low levels and as a result, may be limited to specific manufacturing lines.

- **Constrained manufacturing capacity**. The generic sterile injectable drug industry is highly concentrated and this limited manufacturing

[27]See Department 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), 4.

capacity has been challenged in recent years as the industry has expanded the number of generic products it manufactures. The pressures to produce a 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 when one manufacturer ceases production of a particular drug. For example, manufacturer representatives told us that manufacturing establishments schedule the production of each drug in their product line for specific time periods, often months in advance.[28] An establishment that produces a particular drug may not be able to produce additional quantities in response to a shortage until the next time the particular product is scheduled for production—which could be months after a shortage begins.[29] If a manufacturing establishment has available production capacity, the manufacturer also faces risks when deciding to ramp up production to address a shortage. In particular, one manufacturer representative said that manufacturers do not know how long their competitors will be out of the market. If the manufacturer that left the market quickly restarts production of the drug, the manufacturer that made the investment to ramp up production to address the shortage may face a financial liability if it is unable to sell the additional product it manufactured.

Another capacity-related issue is that the company whose name is on the drug label, which we term the supplier, may or may not be the same as the company that actually manufactures the drug. Rather than produce the drug themselves, some suppliers enter into a relationship with a contract manufacturer to produce the drug on their

[28]We previously found that multiple drugs are often manufactured on the same production line, so increasing production of one drug could reduce the supply of other drugs. For example, one manufacturer representative told us that there are usually anywhere from 30 to 50 different drugs manufactured on a given line. GAO-14-194, 29.

[29]We previously found that it can take as much as 3 months to increase production due to the complexity of manufacturing sterile injectable drugs. In addition to the capacity constraints that result from manufacturing a large number of drugs on only a few manufacturing lines, we previously found that suppliers do not typically have redundant manufacturing facilities. See GAO-14-194, 28-31, for further discussion of this and other capacity constraints.

behalf.[30] Therefore, the number of suppliers of a particular drug may not be the same as the number of manufacturers of that drug.[31] The number of suppliers could also be different than the number of manufacturers if the name on the drug's label is that of a repackager, a distributor, or the parent company of the manufacturer.

## New Drug Shortages Have Decreased Since 2011, but Many Shortages Persist for Multiple Years

New drug shortages continue to be reported, although the number of new shortages each year has generally decreased since 2011. New shortages peaked in 2011 with 257 reported, while 136 new shortages were reported in 2015, a decrease of 47 percent from 2011. Meanwhile, since 2012, the number of ongoing shortages (shortages that began in prior years) has remained high with over 250 ongoing shortages each year from 2012 through 2015.[32] (See fig. 1.) As a result, the majority of drug shortages each year since 2012 have been ongoing shortages rather than newly reported shortages. For example, in 2015, 68 percent of the shortages (291 out of 427) were ongoing shortages that began in a prior year.[33]

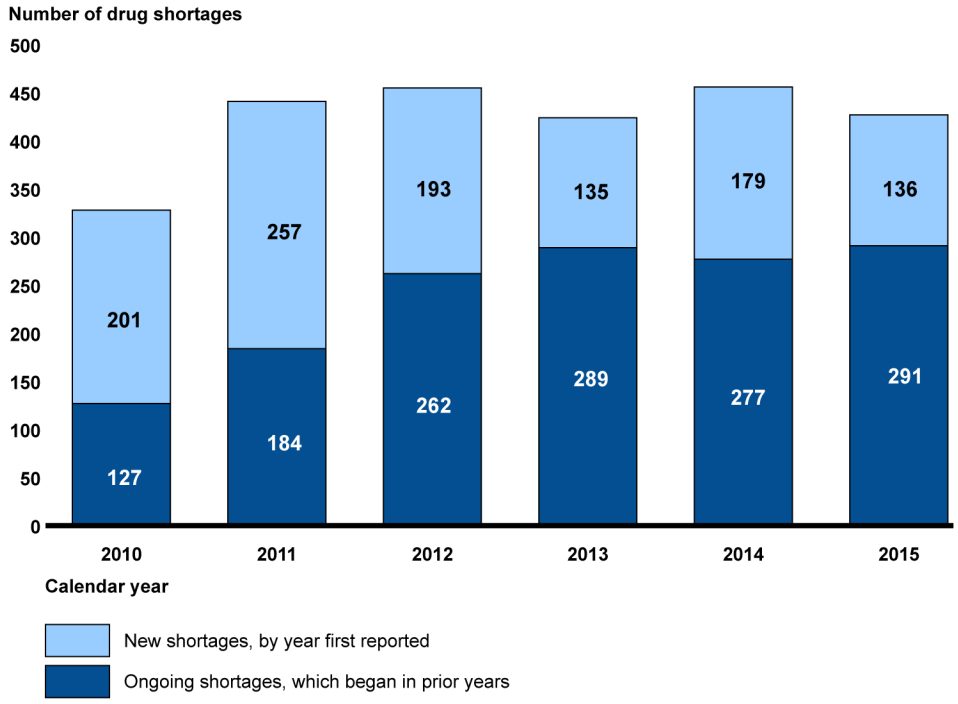
[30]One study found that in the sterile injectable market, drugs produced under contract manufacturing relationships are primarily brand-name drugs marketed by emerging companies without their own manufacturing establishments and that such drugs are generally made by manufacturers that already produce many generic drugs. See J. Woodcock and M. Wosinska, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortages," *Clinical Pharmacology & Therapeutics*, vol. 93, no. 2 (2013), 173.

[31]In addition, a single manufacturer may have multiple manufacturing establishments that produce a given drug.

[32]We counted a shortage as a "new shortage" in the year UUDIS was initially notified of the shortage. We counted a shortage as an "ongoing shortage" in each year that it continued to be in shortage after the year it was first reported. For example, for a shortage of which UUDIS was notified in July 2013 and that continued uninterrupted until its resolution in March 2015 we would count it as a new shortage in 2013 and as an ongoing shortage in both 2014 and 2015.

[33]Though FDA identified far fewer shortages than UUDIS in 2015, the agency reported a similar trend to that seen in the UUDIS data in that new shortages have decreased and the majority of shortages in 2015 were ongoing shortages that began in a prior year. For 2015, FDA identified 26 new shortages and 64 ongoing shortages that began prior to 2015. See appendix I for more information about the differences between FDA's and UUDIS's drug shortage data.

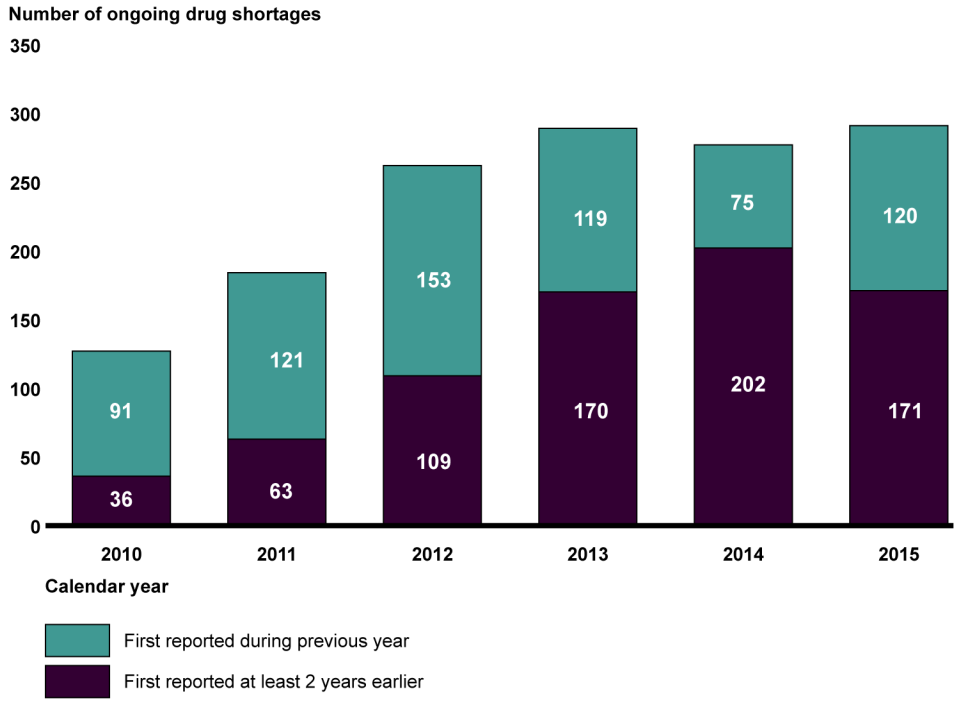
**Figure 1: Number of Drug Shortages from 2010 through 2015**




Source: GAO analysis of University of Utah Drug Information Service data. | GAO-16-595

Since 2013, the majority of the ongoing shortages in a given year were first reported at least 2 years earlier. (See fig. 2.) For example, in 2015, 171 of the 291 ongoing shortages (59 percent) were first reported during 2013 or an earlier year, while the remaining 120 ongoing shortages were first reported during 2014.

**Figure 2: Duration of Ongoing Shortages from 2010 through 2015**




Source: GAO analysis of University of Utah Drug Information Service data. | GAO-16-595

The duration of all shortages reported from January 2010 through December 2015 varied, ranging from 1 day to almost 6 years.[34] Of these shortages, 65 percent lasted 1 year or less, while 12 percent lasted more than 3 years. The average duration of all shortages reported during this time period was 418 days. The fact that some shortages have lasted 3 or more years suggests that manufacturers and FDA have had difficulty addressing the issues behind these persistent shortages. For example, FDA stated that some drugs have been in shortage for multiple years because manufacturers have been unable to address the issues that led to the shortage or have chosen not to continue producing the drugs.

[34]We excluded 30 of the 1,101 shortages reported from January 2010 through December 2015 from this analysis of duration because UUDIS listed these shortages as lasting 0 days. Almost all of these 30 shortages represented manufacturers' decisions to discontinue production of the drug.

The experiences of providers dealing with shortages every day generally supports the trend seen in the UUDIS data that shortages persist. In following up with representatives from the 10 national associations representing health care providers (including hospitals, physicians, and pharmacists) that we contacted for our 2014 report, we learned that shortages continue to affect providers' ability to safely and effectively care for patients.[35] Reflecting on their experiences with shortages in the last 2 years, representatives of 6 of the 10 associations reported that shortages had remained constant or increased, 2 reported a decrease, and 2 others did not identify a trend in recent shortages, but noted that they were still a concern.

## FDA Prioritized Reviews of 383 Submissions to Respond to Drug Shortages

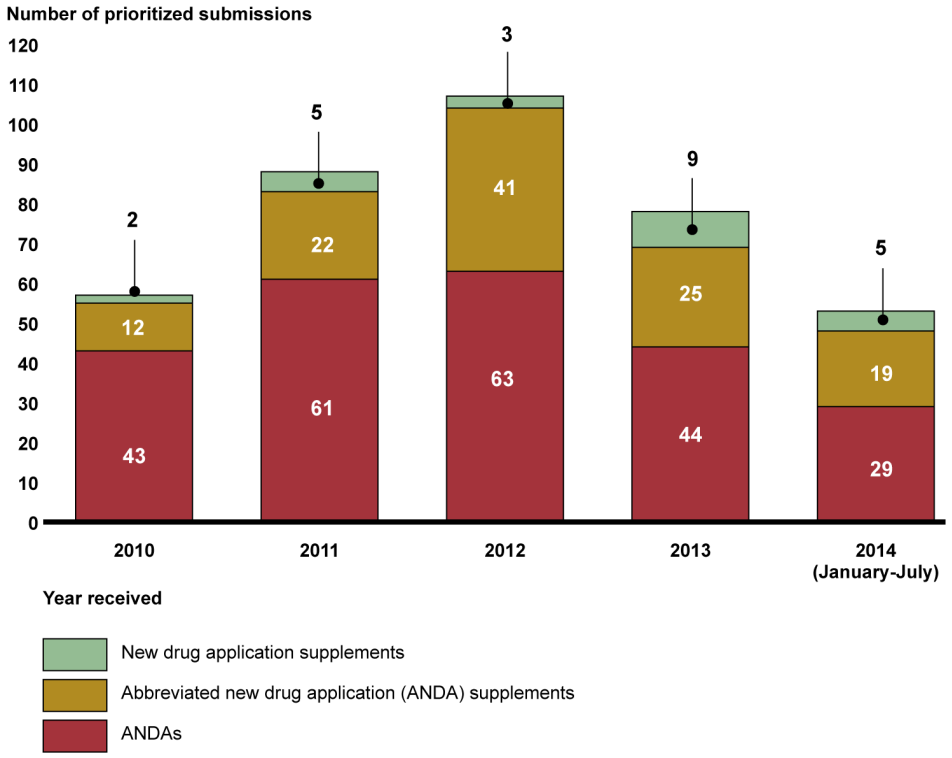
FDA prioritized its review of 383 drug applications and supplements to address shortages from January 2010 through July 2014, 240 of which were for generic sterile injectable drugs. Our analysis of a subset of those submissions indicates that some were approved before the shortage was resolved. Although the timing of FDA's approvals of submissions does not establish a causal link, it could indicate that prioritizing reviews may be a useful strategy in addressing some drug shortages.

### FDA Prioritized Review of Both Drug Applications and Supplements to Address Shortages and the Majority Were for Generic Sterile Injectable Drugs

From January 2010 through July 2014, FDA prioritized its review of 383 submissions—applications and supplements to change approved drug applications—to address drug shortages. These submissions represent 3 percent of all submissions that FDA received during this time period. Almost all of the submissions that FDA prioritized during this time period were ANDAs or ANDA supplements for generic drugs; the remaining few were NDA supplements for brand-name drugs. (See fig. 3.)

[35]GAO-14-194, 18-20.

**Figure 3: Number of Submissions FDA Prioritized Its Review of to Address Drug Shortages, by Submission Type and Year Received, January 2010 through July 2014**




Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-16-595

Further, the majority of the submissions for which FDA prioritized its reviews to address drug shortages were for generic sterile injectable drugs.[36] Specifically, 63 percent (240) of the 383 submissions granted a prioritized review were for generic sterile injectable drugs, and an additional 4 percent (17) were for brand-name sterile injectable drugs. Twenty-four percent (92) of the prioritized submissions were for drugs in capsule or tablet form, while the remaining 9 percent (34) were for drugs in other dosage forms, such as ointments or patches.

[36]This aligns with the characteristics of shortages from recent years as we previously reported that many shortages were of generic sterile injectable drugs. See GAO-14-194, 15, and GAO-12-116, 19.

Overall, FDA had completed at least one review cycle for approximately 80 percent of the 383 prioritized submissions as of October 30, 2014.[37] FDA's review of a submission may span several review cycles before the agency makes a decision regarding its approval, and once the review of a submission is prioritized any subsequent reviews of it are also prioritized. An additional review cycle may occur if, for example, to ensure the safety and efficacy of the product, FDA asks a sponsor to supply additional data, analyses, or other information to address concerns identified in its review.[38] According to FDA it has historically taken, on average, about four review cycles to approve an ANDA. As of October 30, 2014, 43 percent (164) of the 383 prioritized submissions had been approved and FDA had completed at least one review for another 37 percent (140). The majority of submissions for which FDA had not completed a review cycle as of October 2014, were received in 2013 and 2014. See table 1 for the status of the 383 prioritized submissions FDA received from January 2010 through July 2014.

[37]All data on the status of each submission for which FDA had prioritized reviews to address shortages is as of October 30, 2014, which is the date that FDA extracted the data from its database.

[38]For the purposes of this analysis, a complete review cycle includes reviews for which FDA has either issued an approval letter or a complete response letter. A complete response letter is a written communication to a sponsor from FDA usually describing all of the deficiencies that the agency has identified that must be satisfactorily addressed before the submission can be approved. After receiving a complete response letter a sponsor may address the deficiencies identified in the letter and resubmit the submission to FDA for another review.

**Table 1: Status of Submissions FDA Received from January 2010 through July 2014 and Prioritized Its Review of to Address Drug Shortages**

| Status of submission | Number of submissions | Percentage of submissions |
|---|---|---|
| Approved | 164 | 43 |
| FDA completed at least one review cycle | 140 | 37 |
| FDA had not yet completed one review cycle | 64 | 17 |
| Other[a] | 15 | 4 |
| **Total** | **383** | **100[b]** |

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-16-595

Notes: Our analysis does not reflect reviews that FDA completed or approvals made since October 30, 2014.

[a]The other category includes submissions that were withdrawn by the sponsor and ones that FDA refused to receive for review because it determined that such submissions were not sufficiently complete to permit a substantive review.

[b]The percentage column does not sum to 100 due to rounding.

For the submissions in our review that FDA approved as of October 30, 2014, the time from when they were prioritized to approval varied by submission type. These review times ranged from 3 days to more than 3 years for ANDA supplements and from 3 days to 6 months for NDA supplements.[39] For ANDAs, review times ranged from 40 days to more than 3 years.[40] See table 2 for the median time to approval for

[39]One of these ANDA supplements may be an outlier. It was approved more than 3.5 years after its review was prioritized. The ANDA supplement with the next lengthiest time period from prioritization to approval had a time of slightly more than 2 years.

[40]In FDA's Fiscal Year 2015 Generic Drug User Fee Amendments of 2012 Performance Report, FDA reported the average time from initial receipt to approval for all generic drug submissions received in fiscal years 2013 and 2014. For submissions that FDA received in fiscal year 2013, the average time from initial receipt to approval was 738 days for ANDAs and 322 days for ANDA supplements, and for submissions that FDA received in fiscal year 2014 it was 552 days for ANDAs and 226 days for ANDA supplements.

submissions that FDA received and prioritized its review of from January 2010 through July 2014.[41]

**Table 2: Median Time to Approval for Submissions that FDA Received from January 2010 through July 2014 and Prioritized Its Review of to Address Drug Shortages**

| | Days from date prioritized to approval | |
|---|---|---|
| **Submission type (number approved)** | **Median days of FDA review** | **Median days to approval (including FDA review and sponsor follow-up)** |
| Abbreviated new drug application (ANDA) supplements (n=70) | 116 | 117 |
| New drug application supplements (n=12) | 54 | 54 |
| ANDAs (n=71) | 362 | 483 |

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-16-595

Note: Median times to approval were calculated based on 153 of the 164 submissions that were approved as of October 30, 2014. FDA did not provide a date prioritized for 11 of the 164 prioritized submissions that had been approved, so those 11 submissions were excluded from the median times calculated.

If FDA does not approve a submission after the first review, it will provide sponsors with complete response letters seeking additional information that addresses deficiencies that FDA identified, making the time to approval longer. For 47 of the 71 approved ANDAs, FDA issued at least one complete response letter and therefore these ANDAs had more than one review cycle, with a range of two to five cycles. The remaining 24 approved ANDAs were approved at the end of the first review cycle in which they were prioritized. Of the 70 approved ANDA supplements, 52 were approved at the end of the first review cycle in which their review was prioritized, with the number of review cycles ranging from one to three. Of the 12 approved NDA supplements, 11 were approved at the end of the first review cycle that FDA prioritized.

[41]In fiscal year 2013 FDA began phasing in performance goals related to the Generic Drug User Fee Amendments of 2012, including goals related to generic drug submission review times. FDA does not have specific review time goals for the ANDAs and ANDA supplements in our analysis because the agency received all of these submissions prior to fiscal year 2015, the first year that these review time goals were phased in. FDA also has a goal of completing reviews of 90 percent of the substantial backlog of submissions that were pending FDA review at the start of fiscal year 2013 by the end of fiscal year 2017 and many of the submissions in our analysis are part of this backlog.

Lastly, FDA prioritized its review of submissions to address drug shortages for many different sponsors and sometimes for more than one submission per drug during this time period.

- The 383 prioritized submissions came from 107 different sponsors. The number of prioritized submissions for any given sponsor ranged from 1 to 24. The majority of these sponsors (69 percent) had 1 to 2 submissions prioritized, and 9 percent of the sponsors had more than 10 submissions prioritized.

- The 383 prioritized submissions were associated with 160 drugs. The number of submissions for each drug ranged from 1 to 16. Multiple submissions for a single drug were typically from multiple sponsors seeking approval to market the drug. Seventy percent of these drugs were associated with 1 to 2 prioritized submissions, while 6 percent were associated with 7 or more prioritized submissions.

## Analysis of a Subset of Drug Submissions Suggests that Prioritization Can Be Helpful In Preventing or Resolving Some Drug Shortages

Our analysis of a subset of the 383 submissions, consisting of 153 submissions that were associated with 38 drugs, suggests that FDA's prioritization of submissions may be helpful in addressing some drug shortages.[42] To examine this strategy, we reviewed the following:

- **Relationship between submissions and shortage prevention or resolution.** When we examined the subset of prioritized submissions that were associated with 38 drugs, we found that 15 of the drugs were associated with at least one prioritized submission that was approved before the shortage was resolved or a potential shortage was prevented. The timing of FDA's approvals of these submissions suggests that this strategy may have contributed to addressing shortages of these 15 drugs, although it does not establish a causal link. Specifically, the approved submissions for these 15 drugs may have helped resolve 12 shortages, prevent 2 shortages, and mitigate 1 shortage. These approved submissions were for drugs in several therapeutic classes (including anti-infective, oncology, and central nervous system drugs) and used to treat a variety of conditions (including bacterial infections, breast cancer, and attention deficit hyperactivity disorder). Conversely, another 13 of the 38 drugs did not have any prioritized submissions approved prior to the shortage

[42]For these 38 drugs, the number of submissions that FDA prioritized for an individual drug ranged from 1 to 14.

resolution or prevention date, so submissions for those drugs could not have contributed to addressing a shortage. However, for 9 of these 13 drugs at least one prioritized submission was approved after the shortage was resolved or prevented, which FDA determined may have helped to reduce supply vulnerabilities and prevent future shortages. In addition, submissions for 2 of the 38 drugs were not approved as of October 2014 and the shortages the submissions were prioritized to address remained active. Finally, the submissions for 8 of the 38 drugs were not associated with a specific shortage at the time of prioritization, although the majority of these drugs had previously been in shortage or were otherwise vulnerable to shortage. (See table 3.)

**Table 3: Summary of Relationship between Submissions Prioritized by FDA for 38 Selected Drugs and Drug Shortages**

| Relationship to shortages | Number of drugs | Percentage of drugs |
|---|---|---|
| Prioritized submission approved before a shortage was prevented or resolved, which suggests it may have contributed to addressing a shortage[a] | 15 | 39 |
| Shortage prevented or resolved before any prioritized submissions approved that could have helped address the shortage | 13 | 34 |
| No prioritized submissions approved that could have helped address the shortage and shortage was active as of October 30, 2014 | 2 | 5 |
| No active or imminent shortage to address at time of prioritization, but drug vulnerable to shortage | 8 | 21 |
| **Total** | **38** | **100[b]** |

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-16-595

Notes: All data on the status of submissions was as of October 30, 2014. Our analysis does not reflect any reviews that FDA has completed or approvals made that may have occurred since that date.

[a]One of the drugs in this category had a prioritized submission approved that may have helped to mitigate the shortage with which it was associated. However, that shortage remains active.

[b]The percentage column does not sum to 100 due to rounding.

- **Time to approval for approved submissions.** The median time to approval from the date prioritized differed for the 26 submissions that may have contributed to the prevention or resolution of a shortage, compared to the 24 submissions approved after the associated shortage was prevented or resolved.[43] This difference was more

[43]Median times to approval were calculated based on the submissions associated with the subset of 38 drugs that were approved as of October 30, 2014. The time to approval calculation includes both 1) the time that the submission was under review at FDA and 2) any time the submission was with the sponsor, so the sponsor could follow up on deficiencies FDA had identified in its review.

pronounced for ANDAs than for supplements. Specifically, the median time to approval for ANDAs that may have helped to prevent or resolve a shortage was almost 4 months faster than it was for ANDAs that were not approved until after the prevention or resolution of the associated shortage.

- For the 26 submissions that may have contributed to the prevention or resolution of a shortage, the median time to approval was 494 days for ANDAs and 87 days for supplements.[44]

- For the 24 submissions that were not approved until after the associated shortage was prevented or resolved, the median time to approval was 613 days for ANDAs and 80 days for supplements.

Given that the median time to approval for prioritized ANDAs is over a year, prioritizing reviews of ANDAs to address drug shortages is generally not a strategy for addressing shortages in the short term. However, this strategy may be useful to address drug shortages that have persisted across multiple years or recurred multiple times in a few years. This may also be a helpful approach if FDA is notified as early as possible about potential shortages. FDA's drug shortages strategic plan states that early notification of potential supply disruptions is critical because it puts the agency in a better position to use all of its available strategies to address drug shortages, including prioritizing its reviews of ANDAs from sponsors who want to enter the market for a drug that is vulnerable to shortage or already in shortage.[45] The success of this strategy, however, also depends on whether sponsors are willing or able to submit ANDAs for drugs that are vulnerable to shortage or already in shortage, which is beyond FDA's control.

[44]Of the 153 prioritized submissions in the subset we analyzed, 62 were approved as of October 30, 2014. Of these approved submissions, 9 were associated with drugs for which there was no shortage active at the time of prioritization but FDA considered the drugs to be vulnerable to shortage. The median time to approval for these 9 submissions was 895 days for ANDAs and 385 days for supplements. An additional 2 submissions were approved before the shortage of the drug they were associated with even began, so these were not counted as having helped to prevent or resolve a shortage and we did not calculate review times for them. Finally, we also did not calculate a review time for 1 other submission because FDA did not provide the date it prioritized the submission.

[45]See Food and Drug Administration, *Strategic Plan for Preventing and Mitigating Drug Shortages* (October 2013).

# Number of Warning Letters FDA Issued to Sterile Injectable Drug Establishments Increased, Including Letters to Establishments Linked to Widespread Shortages

## Number of Warning Letters FDA Issued to Sterile Injectable Drug Manufacturers Increased, but the Percentage of Inspections Resulting in Letters Was Relatively Small

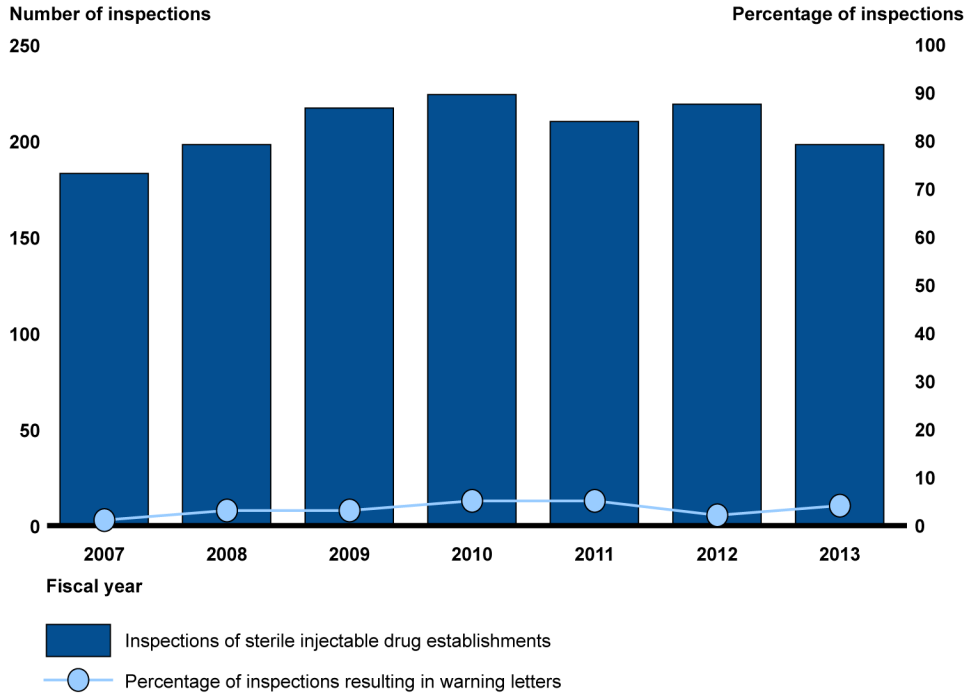
The number of warning letters FDA issued annually to sterile injectable drug manufacturing establishments found to be out of compliance with manufacturing standards generally increased from fiscal year 2007 through fiscal year 2013. The number of letters issued ranged from 1 letter resulting from an inspection conducted in fiscal year 2007, to 11 letters resulting from fiscal year 2010 inspections and another 11 letters resulting from fiscal year 2011 inspections. In addition, FDA issued a growing number of such letters to non-injectable drug establishments, ranging from 16 letters resulting from fiscal year 2007 inspections to 45 letters resulting from fiscal year 2010 inspections and another 45 letters resulting from fiscal year 2011 inspections.[46]

Although the number of warning letters issued increased, the percentage of inspections that resulted in warning letters in a given year remained relatively small. One percent of FDA's fiscal year 2007 inspections of sterile injectable drug establishments resulted in the issuance of warning letters, compared with 5 percent of such inspections in fiscal years 2010

[46]From fiscal year 2007 through 2013, FDA generally increased its inspections of foreign manufacturing establishments. To the extent that foreign establishments were historically inspected less frequently than their domestic counterparts, FDA may have been more likely to identify violations of manufacturing standards when they did conduct inspections at foreign establishments. Warning letters issued to foreign establishments appear to drive the increase in warning letters in some years, but not others.

and 2011. (See fig. 4.) The percentage of inspections of non-injectable drug establishments that resulted in warning letters was similar, ranging from 1 percent of fiscal year 2007 inspections to 4 percent of fiscal year 2013 inspections.

**Figure 4: Number of Sterile Injectable Drug Establishment Inspections and Percentage Resulting in Warning Letters for Noncompliance with Manufacturing Standards, Fiscal Years 2007 through 2013**




Source: GAO analysis of Food and Drug Administration data. | GAO-16-595

As the number of warning letters issued to sterile injectable drug establishments for noncompliance with manufacturing standards generally increased from fiscal year 2007 through fiscal year 2013, so did shortages of these drugs. (See table 4.) Both the number of warning letters and the number of shortages were particularly high in fiscal years 2010 and 2011. While a corresponding rise in warning letters and shortages in certain years could reflect an increase in FDA inspection rigor, as was suggested by some sources in the literature review conducted for our prior report, it could also indicate growing

manufacturing problems.[47] Such problems could lead to shortages as establishments recalled defective products or shut down or slowed production to correct manufacturing problems. What is not known is whether establishments experiencing such manufacturing problems would have shut down or slowed production in the absence of an FDA warning letter.[48]

**Table 4: Number of New Shortages of Sterile Injectable Drugs and Warning Letters Issued to Sterile Injectable Drug Establishments for Noncompliance with Manufacturing Standards, Fiscal Years 2007 through 2013**

| Fiscal year | Number of new shortages | Number of warning letters related to inspections conducted in this fiscal year |
|---|---|---|
| 2007 | 54 | 1 |
| 2008 | 84 | 5 |
| 2009 | 61 | 6 |
| 2010 | 130 | 11 |
| 2011 | 147 | 11 |
| 2012 | 88 | 5 |
| 2013 | 74 | 8 |

Source: GAO analysis of University of Utah Drug Information Service and Food and Drug Administration data. | GAO-16-595

Note: The number of warning letters issued to non-injectable drug establishments for inspections conducted from fiscal year 2007 through 2013, by fiscal year of associated inspection, is as follows: 16, 26, 28, 45, 45, 22, and 42.

FDA officials disputed the notion that the agency's issuance of warning letters to establishments found to be out of compliance with manufacturing standards caused shortages. First, FDA officials noted that some shortages are unrelated to manufacturing problems and therefore could not have been caused by FDA's issuance of warning letters for manufacturing violations. This notion is consistent with our prior analysis of FDA shortage data, which found that from January 2011 through June 2013, 30 percent of shortages were reportedly caused by issues unrelated to manufacturing, such as increased demand or unavailability of

[47]GAO-14-194, 23.

[48]FDA issues warning letters when it identifies violations that, if not promptly and adequately corrected, may lead the agency to take enforcement actions, such as seeking court action to stop an establishment from manufacturing and distributing a product until the violation is corrected.

raw materials or components.[49] Second, although the agency does have other enforcement powers to stop distribution of a product, FDA officials stated that warning letters issued for noncompliance with manufacturing standards do not order a stop in production or distribution.[50] Finally, FDA officials stated that it is important to put warning letter data in perspective by considering the reason that FDA conducted the inspections that resulted in warning letters. According to FDA officials, if the inspections that resulted in warning letters were inspections with a for-cause component and thus were conducted to investigate potential manufacturing problems, then any underlying manufacturing problems that led to the warning letter could also have caused shortages.[51] For example, officials told us that during this time frame, inspections of sterile injectable drug manufacturers were often conducted because of reports of problems with particulates, such as a number of voluntary recalls conducted in response to glass fragments in sterile injectable drugs in 2010 and 2011.[52]

Our analysis of 7 years of FDA data on inspection type does not reveal a clear trend in terms of the relationship between shortages, warning

[49]GAO-14-194, 27.

[50]FDA enforcement actions to stop distribution include denying approval of an application, blocking import entry, seizing or arresting a regulated article before or while in distribution, or working with the Department of Justice to obtain a court order to stop production.

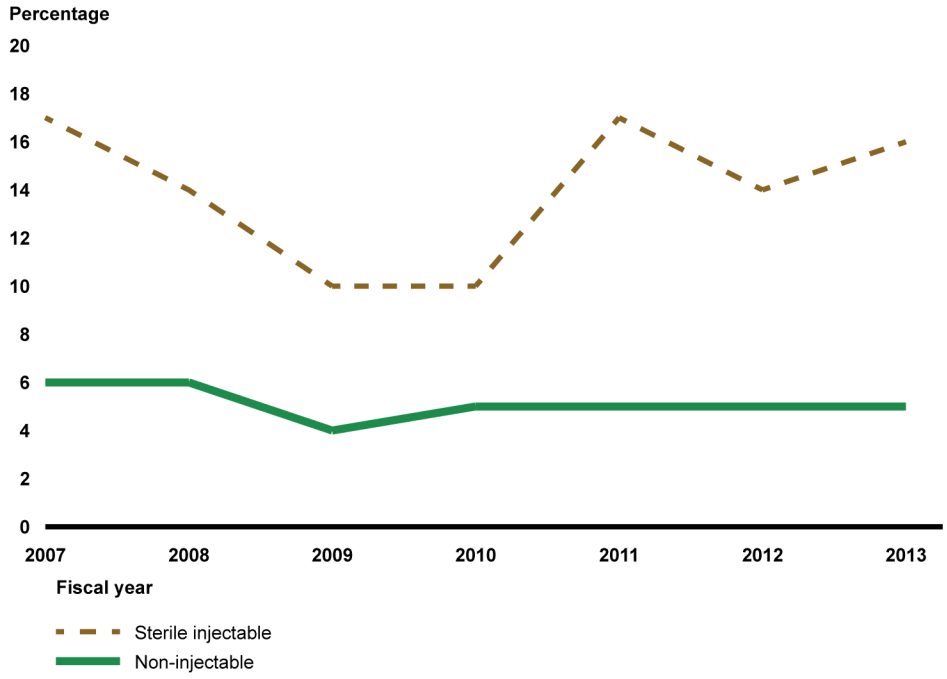
[51]FDA primarily selects establishments for preapproval inspections (conducted as part of its review of applications to market new drugs) or for surveillance inspections (to determine ongoing compliance with laws and regulations in the manufacture of drugs already on the market). However, the agency also initiates for-cause inspections to investigate consumer complaints, reports of product quality defects submitted by consumers or health care professionals, or indications of potential manufacturing problems submitted by the manufacturers themselves through field alert reports, among other reasons. Manufacturers of brand-name and generic drugs are required to submit field alert reports to FDA within 3 working days of receipt of information concerning any bacteriological contamination, any significant chemical, physical, or other change or deterioration in a distributed drug product, any failure of one or more distributed batches of drug product to meet the specifications established for it in the drug application, or any incident that causes the drug product or its labeling to be mistaken for another drug product. 21 C.F.R. § 314.81(b)(1) (2015). According to FDA, the intent of such reports is to establish an early warning system to the agency in order to prevent potential safety hazards.

[52]Our prior analysis of FDA data showed that from January 2011 through June 2013, the reported cause of 40 percent of shortages were quality problems, such as the identification of bacterial contamination or particulate matter. GAO-14-194, 27.

letters, and one indication of potential manufacturing problems—the frequency of inspections with a for-cause component.[53] Our analysis shows that between fiscal years 2007 and 2013 the percentage of inspections with a for-cause component was consistently higher for sterile injectable drug manufacturing establishments than it was for non-injectable establishments. (See fig. 5.) FDA officials told us that they evaluate the health hazards of all reports of potential manufacturing problems that they receive. However, because of the potentially serious health consequences of using a sterile product that has been contaminated, the agency may be more likely to conduct a for-cause inspection in response to reports of potential manufacturing problems at a sterile injectable drug establishment than at one that manufactures non-injectable drugs. Across this time period, the percentage of sterile injectable drug establishment inspections with a for-cause component varied. After declining from its fiscal year 2007 peak, the percentage of sterile injectable drug establishment inspections with a for-cause component grew to 17 percent of fiscal year 2011 inspections. Fiscal year 2011 was also both the peak in new sterile injectable drug shortages and warning letters issued to sterile injectable drug establishments. While the number of warning letters issued to sterile injectable drug establishments was equally high a year earlier in fiscal year 2010 and new shortages were at their second highest, the percentage of inspections with a for-cause component was at its lowest—10 percent. Thus, comparing the trend in inspections with a for-cause component to the trends in shortages and in warning letters provides support for FDA officials' contention that there were underlying manufacturing problems that could have led to shortages and warning letters in some years, but not others.

[53]FDA may conduct an inspection that includes multiple components during a single visit to an establishment. For example, it may follow up on reports of potential manufacturing problems during the for-cause component of an inspection and also verify that the establishment is following commitments made in a drug application during the preapproval component of an inspection.

**Figure 5: Percentage of Inspections with a For-Cause Component, by Establishment Type, Fiscal Year 2007 through Fiscal Year 2013**




Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-16-595

Note: FDA may conduct an inspection that includes multiple components during a single visit to an establishment. Thus, FDA investigators use various codes for reporting the type of inspection conducted in the agency's inspection database. However, FDA officials told us that inspections initiated to follow up on reports of potential manufacturing problems may not be consistently coded as for-cause inspections and instead might be coded as surveillance inspections. Therefore, our counts of inspections with a for-cause component may be an undercount.

## Seven Sterile Injectable Drug Establishments Linked to Widespread Shortages Received Warning Letters and All Had Previous Indications of Difficulty Meeting Manufacturing Standards

From fiscal year 2010 through fiscal year 2012, seven sterile injectable drug manufacturing establishments that received warning letters for noncompliance with manufacturing standards slowed or shut down production. FDA and others said these slowdowns and shutdowns led to widespread shortages. For example, the fiscal year 2012 voluntary shutdown of one of the seven establishments reportedly led to the actual or potential shortage of more than 100 drugs.[54] Another of the seven establishments manufactured more than 300 different drugs, so its production slowdown also led to multiple shortages.

FDA issued warning letters to all seven establishments after finding that the establishments were not in compliance with manufacturing standards during inspections conducted from fiscal year 2007 through fiscal year 2011. Although FDA did not require the establishments to shut down or slow production, the agency noted in a letter to a member of Congress about this issue that when products manufactured under problematic conditions pose a safety threat to patients—such as glass shards or metal shavings in vials of injectable drugs or fungal contamination—manufacturers generally must stop production to resolve the problem.[55] Such problems were experienced by six of the seven establishments linked to widespread shortages when particulates were discovered in their sterile injectable products. For example, a drug at one establishment was found to contain microscopic particles that were “stringy, amorphous, and globular” and sterile injectable drugs at two other establishments contained stainless steel particles. The presence of metal particles in sterile injectable drugs can cause serious injury to patients when injected. Following the receipt of reports of serious injury and illness, a drug manufactured at the seventh establishment was discovered to contain

[54]See, for example, S.L. Kweder and S. Dill, “Drug Shortages: The Cycle of Quantity and Quality,” *Clinical Pharmacology & Therapeutics*, vol. 93, no. 3 (2013), 248.

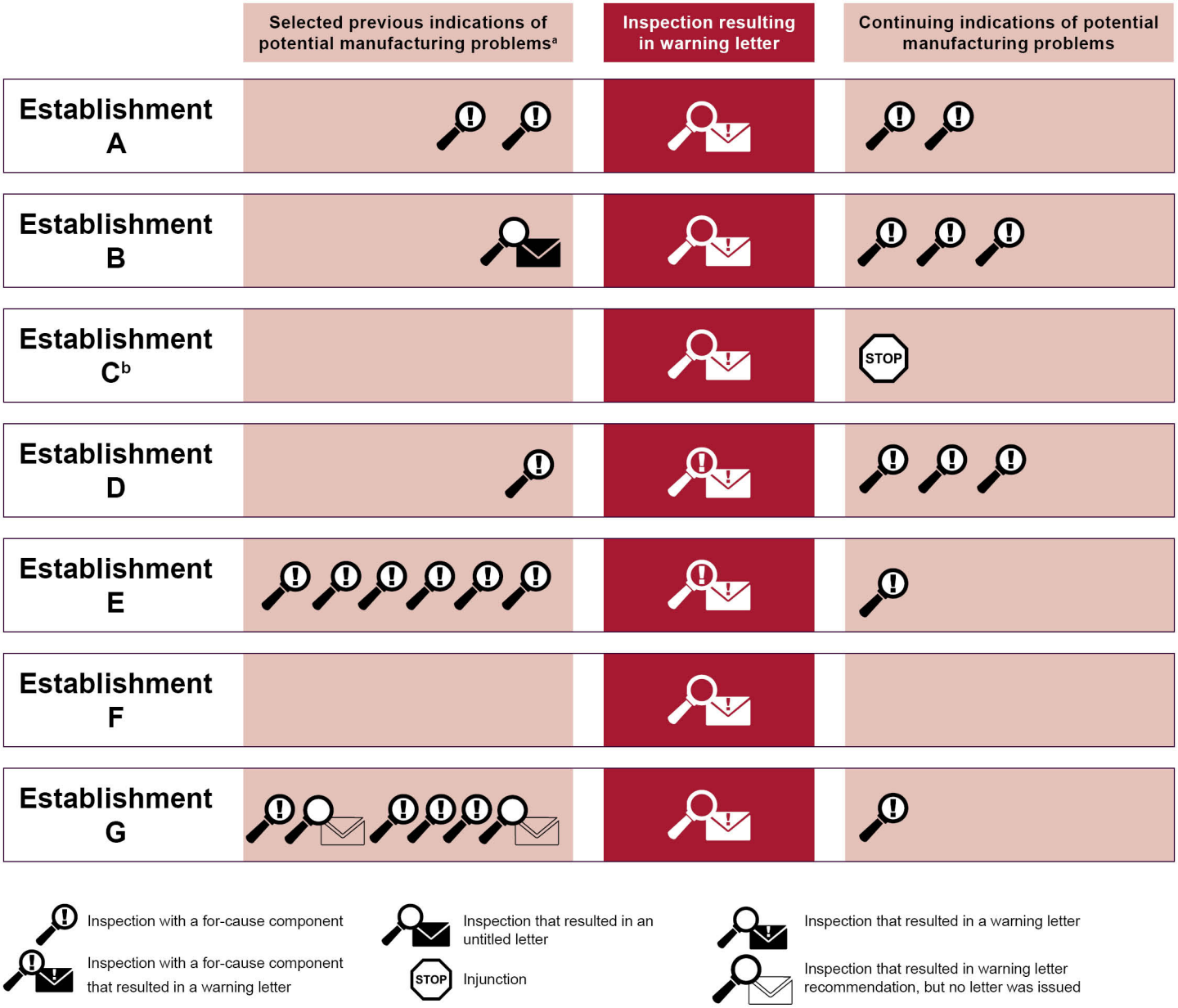
[55]Food and Drug Administration, Letter to the Honorable Elijah E. Cummings, Ranking Member, Committee on Oversight and Government Reform, House of Representatives, July 23, 2012. In this letter, FDA noted that it worked with establishments that received warning letters to try to avoid a shutdown, offering assistance in addressing quality concerns. According to the letter, such assistance involved regular communication to discuss progress in addressing manufacturing issues and help with prioritizing remediation of problems that pose the highest risk to patients. Since 2011, FDA has included language in warning letters requesting that manufacturers contact the agency’s Drug Shortage Staff if the letter results in the manufacturer considering any action that would result in decreased production of drugs.

endotoxin, a component of certain bacteria, which may cause severe fever and death if present in a drug.

FDA documents and data indicate that all seven of these establishments had difficulty meeting manufacturing standards prior to FDA's issuance of a warning letter, which, at least for these establishments, runs counter to the claim that the increase in warning letters was an indication that the agency began to apply manufacturing standards more rigorously. For example, FDA staff previously recommended issuing warning letters to two of the establishments, but after further internal review, FDA issued an untitled letter to one establishment and did not issue a warning letter to the other.[56] (See fig. 6.) For two other establishments, the inspections preceding the inspection that resulted in the warning letter often included a for-cause component. For example, one of the two establishments was inspected six times between fiscal year 2007 and the inspection that resulted in the warning letter and each inspection was conducted in response to manufacturer reports of potential manufacturing problems submitted to FDA, complaints from consumers or health care providers, or both.

[56]Recommendations to issue a warning letter are subject to multiple levels of internal FDA review. In the case of one establishment, FDA ultimately sent an untitled letter, rather than a warning letter. (FDA sends untitled letters when serious violations of manufacturing standards are found, but the violations do not meet the threshold of regulatory significance for a warning letter.) Another establishment was the subject of two previous warning letter recommendations, but during the review process the agency determined that the manufacturer's proposed corrective actions in response to the violations identified during the inspections were adequate and so did not issue the letters.

**Figure 6: Indications of Potential Manufacturing Problems for Seven Establishments Linked to Widespread Shortages, Fiscal Year 2007 through Fiscal Year 2013**




Source: GAO analysis of Food and Drug Administration (FDA) documents and data. | GAO-16-595

Notes:

FDA may conduct an inspection that includes multiple components during a single visit to an establishment (e.g., for-cause component and preapproval component).

FDA issues warning letters when the agency has identified violations that may lead to enforcement action if not promptly and adequately corrected. FDA issues untitled letters when serious violations of manufacturing standards are found, but the violations do not meet the threshold of regulatory significance for a warning letter. FDA may petition a court for an injunction in order to prevent an establishment from manufacturing and distributing drugs until FDA determines that the establishment is compliant with the Food, Drug, and Cosmetic Act.

[a]This figure shows selected indicators of potential manufacturing problems from fiscal year 2007 through fiscal year 2013 only; for example, it does not include information on manufacturing violations that were repeat observations from previous inspections.

[b]For establishment C the inspection that resulted in a warning letter was conducted in fiscal year 2007, so any previous indications of manufacturing problems would have occurred outside of our time frame of fiscal year 2007 through 2013. Our analysis of FDA inspection data shows that FDA conducted inspections with a for-cause component in 3 of the 4 fiscal years preceding the fiscal year 2007 inspection that resulted in a warning letter. FDA officials told us that there were other indications of continuing manufacturing problems at this establishment between the inspection that resulted in the warning letter and the injunction. For example, FDA officials told us that they held three regulatory meetings with the establishment. A regulatory meeting is used to inform establishments about how one or more products, practices, processes, or other activities are considered to be in violation of the law.

Our analysis of FDA documents also shows that, for four establishments, the same manufacturing violations that led FDA to issue a warning letter had also been observed during previous FDA inspections. In the case of one of the four establishments, FDA documents show that the agency had expressed concerns about one violation 5 years prior to the inspection that resulted in the warning letter.

For nearly all of the seven establishments linked to widespread shortages, there were continued indications of difficulty meeting manufacturing standards following their receipt of a warning letter. In addition to issuing one establishment a warning letter, FDA subsequently sought and obtained an injunction against this establishment to prevent it from manufacturing and distributing most drugs until FDA determined that the establishment was compliant with the Food, Drug, and Cosmetic Act.[57] An agency press release about the injunction noted that inspections of the establishment found several product quality problems, including facility cleaning issues and poor equipment maintenance practices resulting in equipment shedding particles into some sterile injectable products. Despite investments to address these issues, this establishment decided to cease manufacturing all drugs and was permanently closed in 2013. Subsequent inspections of four other

[57]The consent decree of permanent injunction entered against the company allowed it to continue to manufacture and distribute certain drugs that FDA had determined were in shortage or vulnerable to shortage. *U.S. v. Ben Venue Labs*., No. 1:13CV154 (N. D. Ohio Jan. 22, 2013).

establishments resulted in the classification of official action indicated, signifying that FDA continued to identify serious deficiencies that warranted regulatory action. With these continued indications of potential manufacturing problems at multiple sterile injectable establishments manufacturing such medically necessary drugs as those used to treat cancer, administer anesthesia, and prevent blood clots, shortages of multiple sterile injectable drugs persist. FDA officials told us that these seven establishments all made improvements and in many cases are now helping to prevent and resolve some shortages. However, as of April 2016, five of these seven establishments continue to cause shortages, according to FDA officials.

## Shortages of Sterile Injectable Anti-infective and Cardiovascular Drugs Were Strongly Associated with Certain Factors

Shortages of sterile injectable anti-infective and cardiovascular drugs during 2012, 2013, and 2014 were strongly associated with certain factors we examined. We estimated a regression model to examine the relationship between drug shortages and four factors: (1) a decrease in the number of suppliers, (2) sales of a generic version, (3) the failure of an establishment making the drug to comply with manufacturing standards resulting in a warning letter, and (4) price decline. We found all factors but price decline to be strongly associated with shortages of the drugs in our study. For each factor, table 5 displays the estimated percentage point increase in the probability of a shortage when the factor is present for all drugs relative to the mean probability of a shortage predicted for all drugs in our study by our model. These estimates show that the presence of a single factor increases the probability of a drug shortage by as much as 16.8 percentage points from what the model otherwise predicts for all drugs in our study.[58]

[58]The mean probability of a shortage predicted by the model for all drugs in our study is 60.7 percent. To compute the mean probability, we first computed the predicted probability of a shortage for every drug and every year in our study by using the estimated coefficients from the model and the data for each drug. We then computed the mean of the 354 predicted values (118 drugs and 3 years), which was 0.607, or 60.7 percent.

**Table 5: Estimated Percentage Point Increase in Probability of a Drug Shortage in the Presence of Certain Factors, for Sterile Injectable Anti-infective and Cardiovascular Drugs, 2012-2014**

The estimated mean probability of a shortage predicted for all drugs in our study by the model is 60.7 percent.

| Factors | Estimated percentage point increase in the probability of a shortage[a] |
|---|---|
| Decrease in suppliers, previous 2 years | 16.8** |
| Sales of a generic version, previous year | 12.3** |
| Failure to comply with manufacturing standards resulting in a warning letter, previous 2 years | 8.1** |
| Price decline, previous 2 years | 0.7 |

Source: GAO analysis of data from IMS Health, the Food and Drug Administration, and the University of Utah Drug Information Service | GAO-16-595.

Notes: Our multivariate logistic regression model uses a 3-year panel data file that contains shortage measures for 118 sterile injectable anti-infective and cardiovascular drugs from 2012 through 2014 and measures of market structure (whether there was a decrease in suppliers), compliance with FDA manufacturing standards (whether there was a failure to comply with manufacturing standards resulting in a warning letter for at least one establishment that manufactured the drug), drug characteristics (whether sales of a generic version), and price and volume of sales (whether the price declined) from 2010 through 2013.

[a]The estimated percentage point increase in the probability of a shortage is calculated as the difference between (1) the probability of a shortage if the factor is present for all drugs and the other three factors remain unchanged and (2) the mean probability of a shortage predicted for all drugs in our study by the model (60.7 percent). To compute the predicted probability of a shortage when the characteristic is present, we set the value of the variable to one, left the values of the other explanatory variables unchanged, and then calculated the probability using the coefficients estimated from our 3-year repeated measures logistic regression model. To compute the mean probability of a shortage predicted for all drugs in our study by the model, we first computed the predicted probability of a shortage for every drug and every year in our study by using the estimated coefficients from the model and the data for each drug. We then computed the mean of the 354 predicted values (118 drugs and 3 years), which was 0.607, or 60.7 percent.

** indicates that the estimated probability is based on a coefficient estimate that was significant at a level of 0.01 or better, based on our logistic regression model results.

The strong association between shortages and both (1) a decrease in the number of suppliers and (2) the failure of an establishment making the drug to comply with manufacturing standards resulting in a warning letter suggests that shortages may be triggered by supply disruptions. Characteristics of the sterile injectable drug industry may make these drugs susceptible to shortage when the number of suppliers decreases. For example, a supplier may decide to permanently discontinue an unprofitable product or the unavailability of raw materials may lead to production delays. Further, failure to comply with manufacturing standards resulting in a warning letter could also trigger a supply disruption if a manufacturer chooses to temporarily shut down production in a particular establishment to correct the conditions that led to a warning letter. In this industry, there is limited inventory in the supply chain, manufacturing capacity is constrained because production is scheduled months in advance, new manufacturers must receive regulatory approval

before entering the market, and the production process is complex. After a supply disruption for any reason, if other manufacturers are not able to increase supply in a timely manner, a shortage may ensue.

For the drugs in our study, the association between noncompliance with manufacturing standards resulting in a warning letter and shortages is largely driven by the structure of the generic injectable manufacturing industry. The warning letters received by three large manufacturing establishments for failure to comply with manufacturing standards appear to be driving our finding that failures to comply with manufacturing standards resulting in warning letters were strongly associated with certain sterile injectable drug shortages.[59] In this industry, establishments produce multiple drugs and so one establishment's failure to comply with manufacturing standards that results in receipt of a warning letter could affect many drugs. For example, 69 percent of the 118 drugs in our study were manufactured by at least one of nine establishments. Thus, if one of these nine establishments failed to comply with manufacturing standards, many drugs in our study could be affected.[60] For example, in 2012 one establishment that failed to comply with manufacturing standards and received a warning letter manufactured 22 drugs in our study. (See table 6.)

[59]These three establishments, in addition to four other establishments that were linked to widespread shortages, were all included in our review of trends in warning letters and each manufactured at least one drug included in the study population for our regression analysis.

[60]This is similar to the findings of another shortages study that found that 6 of the top 10 manufacturers of sterile injectable drugs received warning letters for serious violations of manufacturing standards between 2010 and 2012. S.L. Kweder and S. Dill, "Drug Shortages," 248.

**Table 6: Number of Sterile Injectable Anti-infective and Cardiovascular Drugs Manufactured by Establishments That Failed to Comply with Manufacturing Standards Resulting in a Warning Letter from 2010 through 2013**

| Year | Total number of drugs manufactured at an establishment that received warning letter | Number of establishments that received warning letters | Minimum number of drugs manufactured at an establishment that received warning letter | Maximum number of drugs manufactured at an established that received warning letter |
|---|---|---|---|---|
| 2010 | 32 | 5 | 1 | 21 |
| 2011 | 34 | 6 | 1 | 14 |
| 2012 | 22 | 1 | 22 | 22 |
| 2013 | 26 | 8 | 1 | 9 |

Source: GAO analysis of data from the Food and Drug Administration and IMS Health. I GAO-16-595

Note: Calculations are based on data for a population of 118 sterile injectable anti-infective and cardiovascular drugs. Our calculations of the number of drugs manufactured by establishments that failed to comply with manufacturing standards resulting in a warning letter may be an undercount because we were unable to obtain complete establishment location information for about half of the 118 drugs in our study.

While the strong association between failure to comply with manufacturing standards resulting in the receipt of a warning letter and shortages could support the contention that FDA regulatory activity triggered some shortages, it could also support the contention that there were growing manufacturing problems and possibly related quality concerns that both precipitated the warning letters and led to shortages. The findings of one study indicate that supply disruptions that led to recent shortages of generic sterile injectable drugs were often linked to quality problems.[61] According to this study, quality problems stem from various sources, including insufficient maintenance, outdated or inadequate design of sterile manufacturing processes, and poor oversight that does not test for or respond adequately to indicators of potential quality problems.

Additionally, our finding that sales of a generic version were associated with shortages suggests that relatively low profit margins may also trigger shortages for sterile injectable drugs. Specifically, compared with drugs for which there were only brand-name sales and thus only one supplier, drugs sold generically may have multiple suppliers and relatively lower profit margins. The 88 drugs in our study sold generically were available from an average of four suppliers during 2013, and 10 drugs had eight or more suppliers. Researchers have found that prices, and consequently

[61]Woodcock and Wosinska, “Economic and Technological Drivers,” 171.

profit margins, decline for generic drugs as the number of suppliers increase.[62] Relatively low profit margins may cause suppliers to exit the market for less profitable drugs in favor of more profitable ones or may make it unprofitable to increase supply, which could make the market vulnerable to shortages.

Lastly, though we did not find a price decline in the previous year to be significantly associated with shortages of the anti-infective and cardiovascular drugs in our study from 2012 through 2014, other evidence indicates that price may influence the amount of drugs produced.[63] Research indicates that price influences a supplier's profit margins, which may affect a supplier's decision to stay in the market or invest in the manufacturing establishments.[64] Further, research on shortages in another therapeutic class examined price trends and found that the average price of oncology drugs decreased every year leading up to a shortage, whereas the average price stayed the same or increased for oncology drugs that were not in shortage.[65] (See app. II for more information about our data sources and methodology for our regression model, and app. II, III, and IV for more information about the relationship between certain factors and whether a drug was in shortage.)

[62]See D. Reiffen and M. R. Ward, "Generic Industry Price Dynamics," *The Review of Economics and Statistics*, vol. 87, no. 1, (2005), 37-49 and V. Jensen and B.A. Rappaport, "The Reality of Drug Shortages: The Case of Injectable Agent Propofol," *The New England Journal of Medicine*, vol. 363, no. 9 (2010), 806. Reiffen and Ward found that when the number of generic suppliers increased from 1 to 10, wholesale generic prices fell by approximately 30 percent. They also found that when there are eight or more generic drug suppliers, price falls below long-run marginal costs. When the price of a drug is lower than the long-run cost of producing an additional unit (i.e., its long-run marginal cost), then it is not profitable to increase production.

[63]Our examination of 2013 price data for the drugs in our study found that median prices were lower for drugs in shortage than drugs not in shortage. Specifically, the median price for drugs in shortage with any generic sales was $37.44 less than the median price for such drugs not in shortage. A similar price difference was found for drugs that are brand-name only—drugs in shortage had a median price of $149.64 less than the median price for drugs not in shortage.

[64]Reiffen and Ward, "Generic Industry Price Dynamics" and Jensen and Rappaport, "Reality of Drug Shortages."

[65]Department of Health and Human Services, *Economic Analysis*, 8. This study also found that the volume of sales for oncology drugs declined in the years prior to a drug shortage. This study did not use a regression model to examine whether changes in price were associated with shortages after controlling for other factors that may be associated with shortages.

## Agency and Third-Party Comments and Our Evaluation

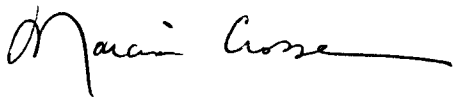
We provided a draft of this report for comment to the Department of Health and Human Services (HHS). We also provided excerpts of this report for comment to UUDIS. We received written comments from HHS, which are reproduced in appendix V. We also received technical comments from HHS and UUDIS, which we incorporated as appropriate.

In its comments, HHS reiterated its commitment to the prevention of new drug shortages and the mitigation and resolution of those shortages that do occur. HHS concurred with our finding that there are still critical shortages affecting the public health. However, in contrast to our finding based on UUDIS data that ongoing shortages remain high, HHS presented FDA drug shortage data indicating that ongoing shortages have decreased. HHS attributed this difference to FDA and UUDIS defining drug shortages differently, which we describe in detail in appendix I of our report. It is important to note that HHS presents FDA's drug shortage data from 2010 through 2015 to describe the decrease in drug shortages, but we have previously identified reliability concerns with these data, which we describe in appendix I. Because of these concerns, we have not used FDA's drug shortage data in our current and previous work, and we instead relied on UUDIS drug shortage data, which we continue to believe are the most comprehensive and reliable information available for the time periods we reviewed. Also, despite the declining trend in both new and ongoing shortages suggested by the FDA drug shortage data, our communications with health care provider organizations suggest that shortages are still a significant concern. Representatives from 8 of the 12 organizations representing health care providers told us that, in their experience, shortages have remained constant or increased.

HHS stated it is not surprising that we identified an association between warning letters and drug shortages, given that the most common cause of drug shortages is manufacturing deficiencies, and that warning letters, by definition, are issued in response to such deficiencies. HHS cautions that this association should not be interpreted as suggesting that warning letters themselves cause shortages. We agree with this note of caution. HHS also noted that our regression analysis may overestimate the direct impact of issuing warning letters because we did not include other measures of manufacturing quality in our model. We considered a number of additional variables in developing our model, some of which are described in appendix II. However, given the size of our study population (118 drugs), we limited the number of variables in our regression analysis. Our model includes key variables grounded in economic theory and findings from our previous work on drug shortages.

We are sending copies of this report to the appropriate congressional committees, the Secretary of HHS, and 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 made key contributions to this report are listed in appendix VI.



Marcia Crosse
Director, Health Care

# Appendix I: Comparison of Drug Shortage Data Collected by the Food and Drug Administration and the University of Utah Drug Information Service

Throughout our work we have received questions from members of Congress about the similarities and differences between the drug shortage data collected by the Food and Drug Administration (FDA) and the University of Utah Drug Information Service (UUDIS). This appendix provides a summary of each data source and the results of a comparison of data from both sources.

## Background

FDA and UUDIS, on behalf of the American Society of Health-System Pharmacists (ASHP), both track and maintain data on drug shortages that occur in the United States. Both organizations make drug shortage information publically available through their respective websites.[1] FDA and UUDIS also maintain drug shortage data that are separate and more comprehensive than the information available on the respective websites. For example, FDA does not post shortages on its website if a shortage is expected to be resolved quickly. Meanwhile, UUDIS only posts information on ASHP's website for a subset of shortages that it deems to be critical.[2]

We have previously conducted analyses of UUDIS drug shortage data to determine trends in the number of drug shortages from January 2001 through June 2013.[3] UUDIS began tracking data on drug shortages in 2001 to inform ASHP's members, such as hospital pharmacists, and other health care providers about the status of new, ongoing, and resolved shortages. These data are generally regarded as the most

[1]For FDA's drug shortage website see http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm. UUDIS posts drug shortage information on ASHP's website; see http://www.ashp.org/menu/DrugShortages.aspx. Additionally, FDA and UUDIS have developed documentation contrasting FDA's and ASHP's drug shortage websites. See http://www.ashp.org/DocLibrary/Policy/DrugShortages/FDA-versus-ASHP.pdf for more information.

[2]UUDIS identifies some shortages as critical because alternative medications are unavailable, the shortages affect multiple manufacturers, or it receives multiple reports from different institutions.

[3]GAO, *Drug Shortages: FDA's Ability to Respond Should Be Strengthened,* GAO-12-116 (Washington, D.C.: Nov. 21, 2011) and *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability,* GAO-14-194 (Washington, D.C.: Feb. 10, 2014). For our 2011 report we analyzed UUDIS drug shortage data from January 1, 2001, through June 20, 2011, while our 2014 report focused on data from January 2007 through June 2013.

comprehensive and reliable source of drug shortage information for the time periods we have reviewed. We used UUDIS data because while conducting work for our 2011 report, we found that FDA did not have a database on drug shortages. While FDA collected some information, it did not lend itself to analysis—it was not easily retrievable, routinely recorded, or sufficiently reliable. Because FDA was unable to provide us with the information necessary to analyze trends in drug shortages, we obtained these data from UUDIS. FDA has since taken steps to track drug shortage data in a systematic manner; it started tracking drug shortages in 2011 in response to our report, and its efforts have evolved over the last several years.[4] However, the data it has compiled since our 2011 report was issued do not include information on shortages prior to 2010.

## Description of FDA and UUDIS Drug Shortage Data

FDA and UUDIS have different definitions of what constitutes a drug shortage. Consequently, they do not always determine the same drugs are in shortage and they do not generally report the same number of shortages overall. Specifically, the Food and Drug Administration Safety and Innovation Act, which FDA implements, defines a drug shortage as a period of time when the demand or projected demand for a drug within the United States exceeds the supply of the drug.[5] In determining whether a shortage exists, FDA focuses on the overall market for a specific drug, meaning that even if a particular manufacturer does not have product available, it is not a shortage if the other manufacturers of that product can meet the projected demand for the whole market. For example, if Manufacturer A has no product available, and Manufacturer B is able to manufacture enough product to satisfy the entire market demand, FDA would not consider this situation a drug shortage, even if Manufacturer B's product is a different strength and package size as long as it views the different sizes and strengths as clinically interchangeable. In contrast, UUDIS 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.

[4]FDA has drug shortage data available from January 2010 through the present. FDA has revised its data collection methods several times since 2011, when it collected information in a spreadsheet. In 2012 FDA developed a drug shortage database and in 2014 it transitioned to a drug shortage data system.

[5]21 U.S.C. § 356c(h)(2).

According to a UUDIS official, the organization therefore focuses on the supply of drugs by national drug code, which is a code that uniquely identifies specific drug products for a given manufacturer.[6] Focusing on the supply of drugs by national drug code means that if one manufacturer does not have enough supply of all strengths and package sizes to meet demand for a period of time it will be considered a shortage. For example, if Manufacturer A has no product available and Manufacturer B has product available—whether it is the same strength and package size or not—UUDIS would consider this to constitute a drug shortage. A UUDIS official said that focusing on supply of a drug by national drug code is important for pharmacists and clinicians because it is the level at which products are ordered and used. Further, the UUDIS official said that substituting one package size for another may create a safety issue. For more information about FDA's and UUDIS's processes for determining whether a drug shortage exists, see table 7.

[6]One drug can have multiple national drug codes associated with it. For example, a drug made by one manufacturer, in one strength, but in three package sizes, would have a different national drug code for each of the three package sizes.

**Table 7: Summary of FDA's and UUDIS's Processes for Identifying and Resolving Drug Shortages**

| | FDA | UUDIS |
|---|---|---|
| Definition of a shortage | A period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug. | 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. |
| How notified of shortage | Manufacturers are required to notify FDA of a discontinuance or interruption in the production of a life-saving drug.[a] In addition, the public and the American Society of Health-System Pharmacists voluntarily file reports on drug availability. FDA also works closely with and regularly communicates with UUDIS. | Voluntary reports from practitioners, patients, pharmaceutical industry representatives, and others. UUDIS also works closely with and regularly communicates with FDA. |
| Standards for determining whether a shortage exists | All manufacturers cannot meet current market demand for the drug based on information provided by manufacturers and market sales research.<br>Shortage is occurring nationwide.<br>Shortage is determined by the supply of the drug at the market level based on information from manufacturers and IMS Health. | Shortage is verified with manufacturers and it affects how a pharmacy prepares or dispenses a product; or the use of alternative drugs is required because of the shortage, which may affect patient care.<br>Shortage is occurring nationwide.<br>Shortage is determined by the supply of a drug by national drug code based on information from manufacturers and providers, according to a UUDIS official. |
| Criteria for resolving shortage | One or more manufacturers are in production and able to meet full market demand. | All manufacturers of the drug restore all strengths and package sizes to full availability or discontinue their products.[b] |

Source: The Food and Drug Administration (FDA) and the University of Utah Drug Information Service (UUDIS). I GAO-16-595

Notes:

[a]21 U.S.C. § 356c. The law 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.

[b]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 notifying UUDIS that Manufacturers B and C have increased supply and all market need has been met.

## Methodology

To compare FDA's and UUDIS's drug shortage data, we reviewed documentation from both FDA and UUDIS. We also analyzed data from both sources related to drug shortages from January 2013 through March 2013.[7] Given our previous finding that shortages last about 9 months to a

[7]Similar to the approach we followed for our prior and current analyses of UUDIS data, we excluded shortages of over-the-counter drugs, biologics (including vaccines), medical devices, and orally-administered vitamins. We did this to ensure that we were comparing shortages of prescription drugs from both data sources.

year on average, we selected this time frame for our comparison to allow for sufficient time for shortages that began during this time frame to have been resolved by the time we started our analysis in July 2014.[8] Data from this time period were also available from both FDA and UUDIS when we started our analysis. Although we considered analyzing data for a more recent time period, FDA did not have reliable drug shortage data readily available from January 2014 through July 2014 when we began our analysis.[9]

We considered an FDA shortage and a UUDIS shortage to be a match if they shared the same active ingredient and route of administration (e.g., hydroxyzine injection) and had some overlapping time period that both were considered to be in shortage. For example, if FDA identified a shortage of a specific drug that began in January 2013 and lasted through December 2013, we considered the UUDIS shortage of the same drug to be a match if it occurred at any point from January 2013 through December 2013. We confirmed the results of our comparison with FDA and UUDIS. For shortages that did not match, we asked both organizations for reasons why one source identified a shortage while the other did not. The purpose of this comparison is to generally illustrate the differences between the two sets of data. The findings of our comparison are not generalizable to drug shortage data from other time periods.

## Comparison of FDA and UUDIS Drug Shortage Data from January 2013 through March 2013

### Number of Drug Shortages Identified by FDA and UUDIS

Our analysis shows that FDA and UUDIS identified a different number of shortages that began from January 2013 through March 2013—17 and 39 respectively. Many of the shortages that FDA identified during this time

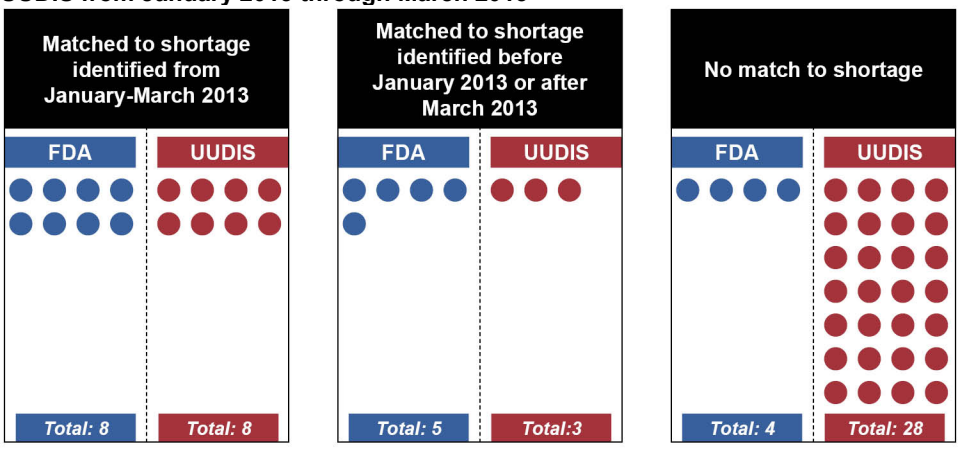
[8]See GAO-14-194, 12, and GAO-12-116, 17.

[9]FDA officials said the agency suspended use of its drug shortage database at the end of 2013 while it was developing a more robust drug shortage data system. According to FDA officials, the transition to the new data system took longer than anticipated and FDA documented limited information about shortages using manual logs during an extended period in 2014. FDA began using this new data system in late 2014, and information on new and active shortages in 2014 was entered retroactively into this system.

period were also identified by UUDIS during this same time period. Specifically, 8 of the 17 shortages that FDA identified as beginning within this time frame matched to a UUDIS shortage that was also identified during the same period. Another 5 of the 17 shortages identified by FDA matched to a UUDIS shortage that was identified as beginning either before January 2013 or after March 2013. The remaining 4 shortages were not identified by UUDIS during any time period.

While many of the shortages identified by FDA during this time period were also identified by UUDIS, our analysis showed the opposite was true for shortages identified by UUDIS. Specifically, most of the 39 shortages UUDIS identified during this timeframe—28 of 39—were not identified as shortages by FDA. Another 3 of the 39 shortages matched to an FDA shortage that was identified as beginning either before January 2013 or after March 2013. (See fig. 7.)

**Figure 7: Comparison of the Number of Drug Shortages Identified by FDA and UUDIS from January 2013 through March 2013**




Source: GAO analysis of Food and Drug Administration (FDA) and University of Utah Drug Information Service (UUDIS) data. | GAO-16-595

Note: From January 2013 through March 2013, FDA identified 17 shortages and UUDIS identified 39. We considered an FDA shortage and a UUDIS shortage to be a match if they shared the same active ingredient and route of administration (e.g., hydroxyzine injection) and had some overlapping time period that both were considered to be in shortage.

For the 8 shortages that both FDA and UUDIS identified from January 2013 through March 2013, we found that in 5 out of 8 instances FDA identified shortages earlier than UUDIS. Also, UUDIS and FDA both had instances of first considering a shortage resolved (in 3 and 5 instances, respectively). (See table 8.) In the 5 instances in which FDA identified a shortage first, the agency identified the shortage between 6 and 50 days prior to UUDIS. In the 1 instance in which UUDIS identified a shortage

first, the organization identified the shortage 13 days prior to FDA. When FDA considered a shortage resolved prior to UUDIS (in 5 out of 8 instances), this determination was made between 23 and 359 days prior to UUDIS. When UUDIS considered a shortage resolved prior to FDA (in 3 out of 8 instances), it reached this conclusion between 67 and 199 days prior to FDA.

**Table 8: Information about the Eight Shortages That Were Identified by Both FDA and UUDIS from January 2013 through March 2013**

| Entity that first identified the shortage | Number of shortages |
|---|---|
| FDA | 5 |
| UUDIS | 1 |
| Same time by UUDIS and FDA | 2 |
| **Entity that first considered the shortage resolved** | |
| FDA | 5 |
| UUDIS | 3 |
| FDA and UUDIS considered resolved at the same time | 0 |

Source: GAO analysis of the Food and Drug Administration (FDA) and the University of Utah Drug Information Service (UUDIS) data. I GAO-16-595

## Reasons Why FDA and UUDIS Shortage Data Often Did Not Match

FDA provided various reasons for why it did not consider 28 of the 39 drug shortages UUDIS identified from January 2013 through March 2013 to be shortages. According to FDA officials, the most common reason is that the agency determined that other manufacturers had the same package size and strength of the drug available. (See table 9.) For example, UUDIS identified a shortage of methylprednisolone sodium succinate injection, a drug used to treat endocrine disorders and allergic reactions, among other things, on January 15, 2013, and considered the shortage resolved on October 23, 2013. UUDIS considered methylprednisolone sodium succinate injection to be a shortage at this time because Manufacturer A discontinued production due to raw material issues, and Manufacturer B had the drug on intermittent back order. Though UUDIS acknowledged that Manufacturer C had this drug available, as did Manufacturer B at times, it posted extensive clinical alternatives on ASHP's website for those providers that were unable to obtain the available drug. FDA did not consider methylprednisolone sodium succinate injection to be in shortage at this time because the agency determined that manufacturers other than Manufacturer A had the same strength and package size of the drug available to meet demand.

**Table 9: Reasons Why FDA Differed with the University of Utah Drug Information Service in Identifying Certain Shortages from January 2013 through March 2013**

| Reason provided by FDA | Number of shortages | Percentage |
|---|---|---|
| Other manufacturers of the same strength and package size had the drug available | 17 | 61 |
| Short term supply disruption | 5 | 18 |
| FDA prevented the shortage | 3 | 11 |
| Alternative strength or package size of the same drug was available | 2 | 7 |
| Different clinically interchangeable drugs were available | 1 | 4 |
| **Total** | **28** | **100** |

Source: Food and Drug Administration (FDA). | GAO-16-595

Note: Percentages do not sum to 100 because of rounding.

Overall, the 28 UUDIS shortages that FDA did not consider to be shortages lasted from 6 days to over 2 years, according to UUDIS's data.[10] In the case of the 5 UUDIS shortages that FDA stated were short-term supply disruptions rather than shortages, the duration ranged from about a month to over 2 years—one shortage was still active as of December 2015. FDA officials described a short-term supply disruption as a situation where manufacturers report a disruption, but that inventory in the supply chain remains available and FDA has not received any reports of shortage from the public. FDA officials said that these types of disruptions commonly involve delays in importing drugs manufactured at foreign establishments or other short-term delays involving transport. FDA also said that it prevented 3 of the 28 shortages that UUDIS identified. According to UUDIS data, those 3 shortages lasted from about 8 months to over 2 years. Lastly, though FDA did not determine that these 28 situations met its criteria to be a drug shortage, UUDIS deemed 13 of these shortages critical, a designation made because alternative medications were unavailable, the shortages affected multiple manufacturers, or the shortages were widely reported.

There were also 4 shortages that FDA identified from January 2013 through March 2013 that UUDIS did not determine to be in shortage. UUDIS did not consider these drugs to be in shortage because it (1) was

[10]One of these 28 shortages was excluded from our analysis of shortage duration because UUDIS listed this shortage as lasting 0 days. The shortage was coded as lasting 0 days because the drug was discontinued by the manufacturer, and thus would not be coming back on the market.

never notified that these drugs were in short supply or (2) heard from suppliers that they had full stock. According to FDA data, these four shortages lasted between 2 months to more than 2 years.

# Appendix II: Scope and Methodology – Relationship between Certain Factors and Sterile Injectable Drug Shortages

To examine the relationship between certain factors and sterile injectable drug shortages, we used economic theory and findings from our previous work on drug shortages to identify factors that may be associated with shortages.[1] We included these factors in a multivariate regression model to determine which factors are associated with shortages.

## Study Population and Data Sources

Our study population included all sterile injectable anti-infective and cardiovascular drugs that were marketed and sold from 2010 through 2014—a total of 118 drugs.[2] We defined a drug to be all products with the same active ingredient and route of administration (e.g., epinephrine injection). We limited the analysis to sterile injectable drugs because we previously found that approximately 65 percent of all critical shortages from January 2009 through June 2013 were for sterile injectable drugs. We selected anti-infective and cardiovascular drugs because in our prior reports we found that approximately one-fourth of all critical drug shortages reported from January 2009 through June 2013 were for drugs in these therapeutic classes.[3] Both anti-infective and cardiovascular drugs continue to be subject to multiple and prolonged shortages.[4] Also, prior studies have focused on other classes, such as oncology.

To identify the drugs in our study population, we used National Sales Perspectives™ data from IMS Health, a company that collects and analyzes health care data. We selected all drugs that were in the anti-infective and cardiovascular Anatomical Therapeutic Classes as listed in the 2014 guidelines from the European Pharmaceutical Market Research

[1]GAO, *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability,* GAO-14-194 (Washington, D.C.: Feb. 10, 2014) and *Drug Shortages: FDA's Ability to Respond Should Be Strengthened,* GAO-12-116 (Washington, D.C.: Nov. 21, 2011).

[2]From a population of all sterile injectable anti-infective and cardiovascular drugs in the National Sales Perspectives™ file with sales between January 2010 and December 2014, we excluded six drugs that were not approved until 2014, and eight drugs that were either discontinued before 2014, used only to dilute another drug, or had sales data of less than $100,000 during our entire study period, but were not in shortage.

[3]GAO-12-116, 21, and GAO-14-194, 17.

[4]As part of our work we spoke to representatives of the American College of Cardiology and the Infectious Diseases Society of America who confirmed that shortages of these drugs have been consistently problematic in recent years.

Association.[5] For each drug, we also used these data to develop annual measures of suppliers, dollar sales, volume sales, and sales for generic and brand-name products.[6] In addition, for each drug we calculated a proxy for average annual transaction price by dividing total dollar sales of the drug by total volume sales.[7]

We used data from the University of Utah Drug Information Service (UUDIS) to determine whether a drug was in shortage during 2012, 2013, and 2014 and when each shortage was first reported to UUDIS. UUDIS 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. For example, UUDIS would consider acyclovir injection to be in shortage if the 20 mL package size was available, but the 10 mL package size was not because health care providers would need to draw out 10 mL doses from a 20 mL vial, which may create a safety issue. In our analysis, drugs classified as being in shortage were in shortage at any time during a given calendar year, and includes shortages that started in a prior year and remained ongoing.

We used drug registration and listing data from the Food and Drug Administration (FDA) to identify the establishments that were listed as manufacturing the drugs in our study population. Using FDA's warning letter data, we then determined whether each drug was manufactured by at least one establishment that failed to comply with manufacturing

[5]The National Sales Perspectives™ data file that we used for this study classifies drugs according to the European Pharmaceutical Market Research Association's Anatomical Classification Guidelines, 2014. These guidelines are available at http://www.ephmra.org/ATC-2014 (accessed May 2, 2016).

[6]We use the term "supplier" to describe the company name on each drug label. The company whose name is on the drug label may or may not be the same as the company that manufactured the drug. A drug's supplier could be different from its manufacturer if the labeler is actually a repackager, a distributor, the parent company of the manufacturer, or if the supplier enters into a contract with another manufacturer—known as a contract manufacturer—to produce the drug on its behalf.

[7]Our method to estimate an average transaction price for each drug has been used by other researchers. For example, see D. Reiffen and M.R. Ward, "Generic Industry Price Dynamics," *The Review of Economics and Statistics*, vol. 87, no. 1 (2005), 37 - 49. We measured volume in terms of eaches, which indicate the number of units for injectable products, such as bottles or injectable vials. We used the Consumer Price Index for all urban consumers to express prices in terms of 2014 dollars.

standards and received a warning letter from FDA at any time in the 2 years before each of the years we examined in our regression analysis. If FDA identifies a violation of law or regulations during an inspection, the agency may then take various regulatory actions, such as issuing a warning letter. FDA issues warning letters when it identifies violations that may lead to enforcement action if not promptly and adequately corrected.

## Regression Model and Panel Data File

We developed an econometric model to examine the association between shortages of sterile injectable anti-infective and cardiovascular drugs and certain factors. Our model uses 3 years of shortage history for each drug in our study to examine the relationship between whether a drug was in shortage during 2012, 2013, or 2014 (dependent variable), and certain factors (the explanatory variables) described below.

To estimate the model we created a panel data file that has three observations, corresponding to 2012, 2013, and 2014, for each of the 118 drugs in our study.[8] Each of the 354 observations contains data on whether the drug was in shortage that year plus data on certain factors pertaining to the preceding 1 or 2 years.

## Dependent Variable: Whether a Drug Was in Shortage

Our dependent variable is a binary variable indicating whether a drug was in shortage during 2012, 2013, or 2014 in a repeated measures model. We selected this time period because, according to UUDIS data, the number of shortages was the highest during 2014, and the number of shortages was also high during 2012 and 2013.[9]

## Explanatory Variables

We developed four categories of factors that may be associated with shortages: drug characteristics, market structure, compliance with

[8]A panel data file is a data set constructed from repeated cross sections of data over time. Our panel data file has three repeated cross sections of data.

[9]We also estimated a model that examined the relationship between shortages that began during 2014 only and certain factors during 2012 and 2013. None of the explanatory variables were statistically significant at a 0.10 level or better. We concluded that none of these explanatory variables were statistically significant in this model because shortages began during 2014 for a relatively small number of drugs in our study (20 out of 118 drugs) and the magnitudes of the correlation coefficients between each explanatory variable and the dependent variable were less than 0.30.

manufacturing standards, and price and volume of sales. Our inclusion of an explanatory variable to measure compliance with manufacturing standards is unique to this study. Our regression model controlled for one factor from each category. We hypothesized that each of the following factors would be positively associated with a shortage in the following year:

- **Generic sales (drug characteristic).** Because drugs sold generically are more likely to have lower profit margins when compared to their brand-name counterparts, we hypothesized that suppliers of such drugs are less likely to increase production in response to a shortage. Drugs sold generically include drugs that had any sales of a generic product, regardless of the presence of any brand product sales. We classified branded generic products as generic products.[10]

- **A decline in the number of suppliers (market structure)**. Such a decline may disrupt the supply of a drug if other suppliers do not increase their production.[11] The number of suppliers for each drug during a year is the number of suppliers that had sales of the drug at any point during that year.[12]

- **Failure to comply with manufacturing standards resulting in a warning letter (compliance with manufacturing standards)**. Manufacturers may choose to temporarily shut down production to correct the conditions that led to the violations of current good manufacturing practice regulations cited in a warning letter. They may also shut down permanently if the costs of correcting the problematic conditions outweigh the potential benefits of producing drugs at that establishment. A drug was associated with a warning letter if at least one establishment manufacturing the drug received a warning letter for failure to comply with manufacturing standards.

[10]A branded generic is a non-originator drug that has never been under patent protection or that was launched after the original patent expired and is marketed under a unique trade name, usually by multiple manufacturers.

[11]For our regression model we considered two factors related to market structure: whether the number of suppliers declined and whether there was more than one supplier. Some regression specifications included whether the number of suppliers declined and others included whether there was more than one supplier. The first factor was statistically significant, but the second was not.

[12]Our annual supplier counts do not include suppliers with missing names in the IMS Health data.

- **Price decline (price and volume of sales)**. Shortages may occur if prices decline because suppliers will not have a financial incentive to increase production of the drug in shortage. For each drug, we calculated a proxy for the average annual price as the ratio of its total dollar sales to its total volume sales. We adjusted all prices to 2014 dollars using the Consumer Price Index for all urban consumers.

## Model Specification

We used our 3-year panel data file to estimate a repeated measures logistic regression model in which the dependent variable was a binary variable indicating whether there was a new or ongoing drug shortage in the given year (2012, 2013, or 2014).[13] The model included the following binary explanatory variables for whether:

- there were sales of the drug in its generic or branded generic form during the previous year,
- the number of suppliers of the drug was greater 2 years before the given year compared with 1 year before it,
- the proxied average price of the drug was greater 2 years before the given year compared with 1 year before it, and
- an establishment that manufactured the drug failed to comply with manufacturing standards and received a warning letter from the FDA in either of the preceding 2 years.

We used the coefficient estimates from the repeated measures logistic regression model to calculate for each explanatory variable the estimated percentage point increase in the probability of a shortage when the explanatory variable is present for all drugs relative to the mean probability of a shortage predicted for all drugs in our study by our model. We did this in three steps. First, for each explanatory variable, we estimated the probability of a shortage in the presence of that variable by setting the value of the variable to one, leaving the values of the other explanatory variables unchanged, and then calculated the probability. Second, we used the coefficient estimates from the regression model and

[13]The estimating method is generalized estimating equations. See Paul Alison, *Logistic Regression Using SAS®: Theory and Application,* 2nd ed., (Cary, N.C.: SAS Institute, Inc., 2012), section 8.4. We estimated the model with SAS software and used the SAS GENMOD procedure. The quasilikelihood under the independence criterion goodness of fit measure for our estimated regression model was 377.

the data for every drug in our study to calculate the mean probability of shortage predicted for all the drugs in our study, which was 0.607. Third, to compute the estimated percentage point increase in probability of a shortage for each explanatory variable, we computed the difference between the probability of a shortage for each explanatory variable (step 1) and the mean probability of a shortage predicted for all drugs in our study (step 2).Table 10 presents the coefficients (log odds ratios) and odds ratios we estimated from our repeated measures logistic regression model.

**Table 10: Estimated Odds Ratios from Repeated Measures Logistic Regression Model of Shortages for Sterile Injectable Anti-infective and Cardiovascular Drugs, 2012-2014**

| Characteristic | Estimated log odds ratio (standard error) | Estimated odds ratio |
|---|---|---|
| Sales of a generic version, previous year | 1.86** (0.36) | 6.4** |
| Decrease in suppliers, previous 2 years | 1.14** (0.41) | 3.1** |
| Failure to comply with manufacturing standards, resulting in the receipt of FDA warning letter, previous 2 years | 0.67** (0.22) | 2.0** |
| Price decline, previous year | 0.08 (0.19) | 1.1 |

Source: GAO analysis of data from IMS Health, the Food and Drug Administration, and the University of Utah Drug Information Service | GAO-16-595.

Notes:

We estimated a repeated measures logistic regression model with generalized estimating equations. The data are from a 3-year panel data file that includes shortage measures for 118 sterile injectable anti-infective and cardiovascular drugs from 2012 through 2014 and measures of drug characteristics (sales of a generic version), market structure (decrease in suppliers), compliance with FDA manufacturing standards (failure to comply with manufacturing standards resulting in receipt of a warning letter), and price and volume of sales (price decline) from 2010 through 2013. The model includes a set of binary variables for the years 2012 through 2014.

** indicates that the estimated probability was significant at a level of 0.01 or better. The quasilikelihood under the independence criterion goodness of fit measure is 377.

For each explanatory variable, the estimated probability of a shortage if that variable is present for every drug in our study is presented in table 11.

**Table 11: Estimated Probability of a Drug Shortage When Each Explanatory Variable Is Present, Sterile Injectable Anti-infective and Cardiovascular Drugs, 2012-2014**

The estimated mean probability of a shortage predicted for all drugs in our study by the model is 0.607.[a]

| Characteristic | Estimated probability of a shortage if characteristic present[b] |
|---|---|
| Sales of a generic version, previous year | 0.730** |
| Decrease in suppliers, previous 2 years | 0.775** |
| Failure to comply with manufacturing standards resulting in the receipt of an FDA warning letter, previous 2 years | 0.688** |
| Price decline, previous 2 years | 0.614 |

Source: GAO analysis of data from IMS Health, the Food and Drug Administration, and the University of Utah Drug Information Service | GAO-16-595.

Notes: We calculated these estimates using the coefficients we estimated from a repeated measures logistic regression model. We estimated the regression model with a 3-year panel data file that includes shortage measures for 118 sterile injectable anti-infective and cardiovascular drugs from 2012 through 2014 and measures of drug characteristics (sales of a generic version), market structure (decrease in suppliers), compliance with FDA manufacturing standards (failure to comply with manufacturing standards resulting in receipt of a warning letter), and price and volume of sales (price decline) from 2010 through 2013.

[a]To compute the mean probability of a shortage predicted for all drugs in our study by the model, we first computed the predicted probability of a shortage for every drug and every year in our study by using the estimated coefficients from the model and the data for each drug. We then computed the mean of the 354 predicted values (118 drugs and 3 years), which was 0.607, or 60.7 percent.

[b]To compute the predicted probability of a shortage when the characteristic is present, we set the value of the variable to one, left the values of the other explanatory variables unchanged, and then calculated the probability using the coefficients estimated from our 3-year repeated measures logistic regression model.

** indicates that the estimated probability is based on a coefficient estimate that was significant at a level of 0.01 or better, based on our repeated measures logistic regression model results.

## Additional Factors

To inform our selection of the explanatory variables to include in the regression model, we computed descriptive statistics for a broad range of factors in the following categories: drug characteristics, market structure, compliance with FDA manufacturing standards, and price and volume of sales. Specifically, we compared frequencies, medians, and trends over time for these factors for drugs in shortage and those not in shortage during 2014. Some of the additional factors that we analyzed were:

- **Years since brand-name or generic drug approval (drug characteristic).** The years since brand-name drug approval is based on the date of the oldest approved new drug application associated

with a particular drug. The years since generic drug approval is based on the oldest approved abbreviated new drug application associated with a particular drug. Both of these measures truncate at 32 years because FDA's data source for approval history—Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)—does not provide approval dates before 1982.

- **Number of establishments that manufacture the drug (market structure)**. We used FDA drug registration and listing data from 2009 and 2014 to identify the number of establishments that were listed as manufacturing the drugs in our study. As many establishments manufacture more than one drug, we also created a measure that identifies the relationship between the establishments and all of the drugs in our analysis.

- **Receipt of an official action indicated inspection classification (compliance with manufacturing standards).** FDA classifies establishment inspections as official action indicated when serious deficiencies are found that warrant regulatory action. When an inspection is so classified, FDA may take various regulatory actions, including issuing a warning letter, which we include in our regression model.

## Limitations

Our analysis has some limitations. First, our findings are limited to data for sterile injectable anti-infective and cardiovascular drugs that were marketed and sold from 2010 through 2014 and shortages in these two therapeutic classes from 2012 through 2014. Our findings are not generalizable to drugs in other routes of administration, other therapeutic classes, or shortages during other time periods. Second, missing manufacturing location data may have caused us to underestimate or overestimate the relationship between shortages and noncompliance with manufacturing standards resulting in a warning letter. For the drugs in our study that were missing manufacturing location data, we could not always identify whether the drugs were manufactured by at least one establishment that received a warning letter. Therefore, we may have misclassified some drugs that were manufactured by establishments that received a warning letter as drugs manufactured by establishments that did not receive a warning letter. Whether we may have overestimated or underestimated the relationship depends on whether the potentially misclassified drugs were in shortage. If these potentially misclassified drugs were in shortage, our model may underestimate the relationship between shortages and receipt of a warning letter. If these potentially misclassified drugs were not in shortage, our model may overestimate the

relationship between shortages and receipt of a warning letter. The extent to which we may have underestimated or overestimated this relationship is unclear. For 57 of the 118 drugs in our study, we found partial manufacturing location data, and for 3 drugs we found no manufacturing location data. We were not able to identify these data for drugs if the IMS data did not include a national drug code for a particular product or if the manufacturer was not listed in FDA's drug registration and listing data. Finally, our proxy for average transaction price for the drugs in our study applies to all strengths and package sizes of the drug, because we defined a drug to include all products with the same active ingredient and route of administration, regardless of strength or package size. We used this definition of a drug because it is the definition that UUDIS uses to record drug shortages. In the market, average transaction prices for each drug vary by strength and package size.

## Data Reliability and Audit Standards

We took several steps to ensure that the data used to produce this analysis were sufficiently reliable. Specifically, we assessed the reliability of the IMS Health National Sales Perspectives™ data by interviewing officials at IMS Health. We also reviewed relevant documentation and examined the data for obvious errors, such as missing values and values outside of expected ranges. We assessed the reliability of the UUDIS and FDA data by interviewing officials, reviewing relevant documentation, and examining the data for obvious errors. We determined that these data were sufficiently reliable for the purposes of this analysis.

# Appendix III: Comparison of Selected Factors for Sterile Injectable Anti-infective and Cardiovascular Drugs by Shortage Status, 2012 - 2014

This appendix compares certain factors for sterile injectable anti-infective and cardiovascular drugs in shortage during 2012, 2013, and 2014 to those same factors for drugs not in shortage during those years. Drugs classified as being in shortage during a year were in shortage anytime during that year, and include shortages that started in a prior year and remained ongoing. In general, we found differences between drugs that were in shortage during this time period and drugs that were not in shortage (see table 12). For example, our analysis showed that for 19 to 23 percent of these drugs in shortage between 2012 and 2014, the number of suppliers decreased during the 2-year period before the shortage compared with 6 percent or less of drugs that were not in shortage. A decline in the number of suppliers indicates that a supplier that had sales for a particular drug in one year had no sales for that drug in the next.

**Table 12: Relationship between Certain Factors and Shortages of Sterile Injectable Anti-infective and Cardiovascular Drugs, by Shortage Status in 2012-2014**

| Shortage year and factors during prior year(s) | Percentage for drugs in shortage | Percentage for drugs not in shortage |
|---|---|---|
| **Shortage, 2014** | | |
| Decrease in suppliers, 2012-2013 | 23.3 | 4.4 |
| Failure to comply with manufacturing standards resulting in a warning letter, 2012-2013 | 46.6 | 13.3 |
| Sales of a generic version, 2013 | 90.4 | 35.6 |
| Price decline, 2012-2013 | 46.6 | 33.3 |
| **Shortage, 2013** | | |
| Decrease in suppliers, 2011-2012 | 21.7 | 6.1 |
| Failure to comply with manufacturing standards resulting in a warning letter, 2011-2012 | 55.1 | 12.2 |
| Sales of a generic version, 2012 | 85.5 | 49.0 |
| Price decline, 2011-2012 | 43.5 | 44.9 |
| **Shortage, 2012** | | |
| Decrease in suppliers, 2010-2011 | 18.6 | 2.1 |
| Failure to comply with manufacturing standards resulting in a warning letter, 2010-2011 | 52.9 | 16.7 |
| Sales of a generic version, 2011 | 90.0 | 45.8 |
| Price decline, 2010-2011 | 67.1 | 43.8 |

Source: GAO analysis of data from IMS Health, the Food and Drug Administration, and the University of Utah Drug Information Service. | GAO-16-595

Notes: Calculations are based on data for a population of 118 sterile injectable anti-infective and cardiovascular drugs. There were 73 drugs in shortage during 2014, 69 during 2013, and 70 during 2012.

We use the term “supplier” to describe the company name based on the drug label.

For drugs with sales of a generic version, either both brand and generic versions of the drug were sold or only generic versions were sold.

Prices were calculated by dividing total dollar sales by total volume sales. Prices were adjusted to 2014 dollars using the Consumer Price Index for all urban consumers.

# Appendix IV: Comparison of Selected Factors for Sterile Injectable Anti-infective and Cardiovascular Drugs by Shortage Status in 2014

This appendix compares certain factors for sterile injectable anti-infective and cardiovascular drugs in shortage in 2014 to those same factors for drugs not in shortage that year. Drugs classified as being in shortage were in shortage anytime during 2014, and include shortages that started in a prior year and remained ongoing. In general, we found differences between drugs that were in shortage and not in shortage in 2014 for certain factors, such as for sales of generic versions of the drug (see table 13).

**Table 13: Certain Factors Associated with Sterile Injectable Anti-infective and Cardiovascular Drugs, by Shortage Status in 2014**

| | Year(s) | In shortage, 2014 | Not in shortage, 2014 |
|---|---|---|---|
| **Drug characteristics** | | | |
| Sales of only generic versions of the drug | 2010-2014 | 51% | 18% |
| Sales of both brand-name and generic versions of the drug | 2010-2014 | 47% | 20% |
| Sales of only brand-name versions of the drug | 2010-2014 | 3% | 62% |
| Median years since brand-name drug approval[a] | 2013 | 31 | 14 |
| Median years since generic drug approval[a] | 2013 | 21 | 0 |
| **Price and volume of sales[b]** | | | |
| Median change in annual price | 2010-11 | -5.3% | 1.1% |
| | 2011-12 | -0.5% | 2.3% |
| | 2012-13 | 0.5% | 4.4% |
| | 2013-14 | 0.4% | 6.3% |
| Median change in annual volume sales | 2010-11 | -2.1% | -4.7% |
| | 2011-12 | -4.6% | -4.5% |
| | 2012-13 | -2.2% | -5.6% |
| | 2013-14 | 2.3% | -3.3% |
| **Market structure** | | | |
| Percentage of drugs with generic sales: | | | |
| 1 supplier with sales | 2013 | 10% | 9% |
| 2 - 4 suppliers with sales | | 36% | 8% |
| 5 or more suppliers with sales | | 30% | 2% |
| Missing supplier data[c] | | 5% | 0% |
| Percentage of drugs with brand-name only sales: | 2013 | | |
| 1 supplier with sales | | 7% | 93% |
| 2 or more suppliers with sales | | 0% | 0% |
| Missing supplier data[c] | | 0% | 0% |
| Median market share of largest supplier with sales | 2013 | 75% | 100% |

| | Year(s) | In shortage, 2014 | Not in shortage, 2014 |
|---|---|---|---|
| Median number of establishments that manufacture the drugs | | 5 | 2 |
| Drugs manufactured at an establishment that manufactures at least 10 percent of the drugs in our study | | 88% | 36% |
| **Compliance with FDA manufacturing standards[d]** | | | |
| Percentage of drugs manufactured by at least one establishment that received an inspection classified as official action indicated | 2012-2013 | 89% | 33% |
| Percentage of drugs manufactured by at least one establishment that failed to comply with manufacturing standards and received a warning letter | 2012-2013 | 47% | 13% |

Source: GAO analysis of data from IMS Health, Food and Drug Administration (FDA), and University of Utah Drug Information Service. | GAO-16-595

Notes: Calculations are based on data for a population of 118 sterile injectable anti-infective and cardiovascular drugs. In 2014, 73 of the 118 drugs in our study were in shortage. Twenty of these shortages began in 2014 and the remaining 53 began in prior years.

We use the term supplier to describe the different company names based on the drug label.

We used FDA drug registration and listing data from 2009 and 2014 to identify the number of establishments that were listed as manufacturing the drugs in our study. Our calculations of the number of establishments that manufacture a particular drug and the number of drugs manufactured by an establishment that received an official action indicated inspection classification or a warning letter may be an undercount because we were unable to obtain complete establishment location information for about half of the 118 drugs in our study.

[a]The years since brand-name drug approval is based on the date of the oldest approved new drug application associated with a particular drug. The years since generic drug approval is based on the oldest approved abbreviated new drug application associated with a particular drug. Both of these measures truncate at 32 years because FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) data do not provide approval dates before 1982. Thus, we report the median for both of these measures.

[b]Prices were calculated by dividing total dollar sales by total volume sales. We report median changes in annual prices instead of mean changes because for some years, a price increase for one drug upwardly skewed the mean change in price. Prices were adjusted to 2014 dollars using the Consumer Price Index for all urban consumers.

[c]Supplier data were missing if the supplier name was missing in the IMS data or if there were no sales of the drug in 2013.

[d]FDA classifies establishment inspections as official action indicated when serious deficiencies are found that warrant regulatory action. When an inspection is classified as official action indicated, FDA may take various regulatory actions, including issuing a warning letter. Thus, some of the drugs included in the official action indicated percentage calculation are the same drugs in the warning letter calculation.

# 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

JUN 08 2016

Ms. 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: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge"* (GAO-16-595).

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

Sincerely,

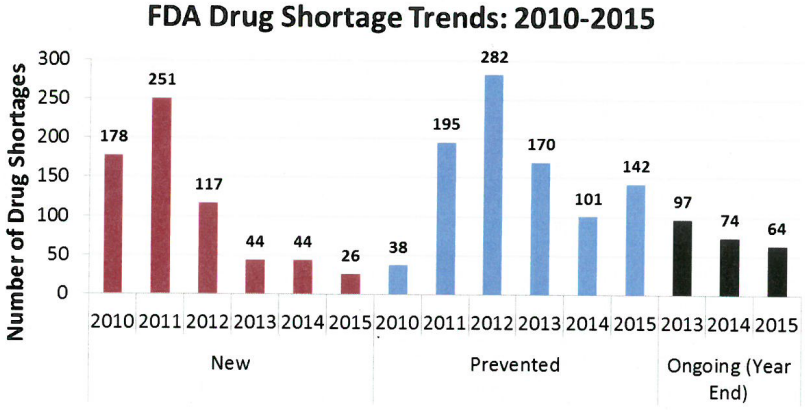
Jim R. Esquea
Assistant Secretary for Legislation

Attachment

**THE DEPARTMENT OF HEALTH AND HUMAN SERVICES' (HHS) GENERAL COMMENTS TO THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED "DRUG SHORTAGES: CERTAIN FACTORS ARE STRONGLY ASSOCIATED WITH THIS PERSISTENT PUBLIC HEALTH CHALLENGE" (GAO-16-595)**

The Department of Health and Human Services appreciates the opportunity to review and comment on this draft report. HHS is committed to the prevention of new drug shortages and the mitigation and resolution of ongoing ones. Notification requirements put into place by Executive Order 13588 in 2011 and the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012 have helped FDA learn about potential shortages from manufacturers earlier so that FDA may take steps to address the shortage, such as expediting the review of an application or supplement or working with manufacturers to prevent shortages or mitigate the impact of unavoidable shortages.

As the report acknowledges, FDA and the University of Utah Drug Information Service (UUDIS) have different definitions of what constitutes a drug shortage, which leads to differences in data since the UUDIS definition counts a situation in which not all National Drug Codes have been restored by all manufacturers as an ongoing shortage. In contrast, FDA takes a more public health-oriented approach and determines whether total demand is being met at a national level. If alternative versions of the drug in shortage are judged by medical staff to be an appropriate substitute and are able to meet national demand, FDA considers the shortage resolved. While we recognize that there are still critical shortages impacting the public health, as the figure below illustrates, new drug shortages have decreased significantly since 2011 and ongoing shortages are declining similarly.

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**THE DEPARTMENT OF HEALTH AND HUMAN SERVICES' (HHS) GENERAL COMMENTS TO THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED "DRUG SHORTAGES: CERTAIN FACTORS ARE STRONGLY ASSOCIATED WITH THIS PERSISTENT PUBLIC HEALTH CHALLENGE" (GAO-16-595)**

The decline in new and ongoing shortages in recent years is, in our view, a reflection of FDA's success in preventing and resolving drug shortages. The data also show that in recent years, FDA has prevented at least 100 drug shortages annually.

One focus of GAO's report is the potential relationship between Warning Letters and drug shortages. Warning Letters are issued for significant deficiencies that can adversely impact product quality, and they provide notification to industry that the deficiencies need to be addressed. HHS is not, therefore, surprised that GAO detected an association between Warning Letters and drug shortages, because these letters are frequently issued for manufacturing deficiencies, the most common cause of drug shortages.

Since, by their nature, Warning Letters react to manufacturing issues, HHS questions any suggestion that the Warning Letters are causing the shortages. Excluding other factors that relate to manufacturing quality from the regression analysis, such as whether a manufacturing facility's inspection had a for-cause component, may lead the model to overestimate the direct impact of issuing Warning Letters. Furthermore, GAO's analysis does not permit a separate assessment of the impact of the underlying manufacturing quality problems. While HHS appreciates that GAO has included some of these caveats in the body of its report, these issues are still left unaddressed in other major sections, such as the report summary.

In any event, the significant deficiencies identified by Warning Letters in recent years have represented significant risks to the public health, including endotoxin contamination, which may cause severe fever and death; the presence of metal particles in sterile drugs, which can cause serious injury to patients if injected; and overfill of vials, which could result in caregivers administering an accidental overdose to patients. FDA works closely with manufacturers to help resolve deficiencies as quickly as possible, and, in appropriate cases, exercises regulatory flexibility to prevent or address shortages. However, FDA alone cannot address these problems. The GAO report affirms FDA's longstanding position that drug manufacturing firms must have a commitment to quality. Failure to do so can result in drug shortages putting patient care at risk. As the report discusses, some facilities have had a great deal of trouble meeting quality standards, even with the Agency's help, or have determined voluntarily that they had to slow or stop production of drugs to address serious quality problems.

HHS also agrees with GAO's statement that the relatively low profit margins of generic drugs may be linked to drug shortages. The low return on investment creates an environment in which manufacturers may not reinvest in manufacturing capacity, infrastructure, and quality, which is a cause of drug shortages. Also, in many cases, manufacturers that make multiple products are less likely to increase production of older generics that fall into shortage; they are more interested in committing available resources to newer products, which are generally more profitable.

**THE DEPARTMENT OF HEALTH AND HUMAN SERVICES' (HHS) GENERAL COMMENTS TO THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED "DRUG SHORTAGES: CERTAIN FACTORS ARE STRONGLY ASSOCIATED WITH THIS PERSISTENT PUBLIC HEALTH CHALLENGE" (GAO-16-595)**

Finally, while much progress has already been made in preventing and mitigating drug shortages, FDA seeks to continue reducing the incidence and impacts of drug shortages. FDA is committed to working with firms, healthcare providers, regulators, and other stakeholders to find ways to address the root causes of drug shortages and to ensure a stable supply of critical medicines. The GAO report represents an important step in highlighting some of the economic factors that make it challenging for FDA alone to address this problem.

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# Appendix VI: GAO Contact and Staff Acknowledgments

## GAO Contact

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## Staff Acknowledgments

In addition to the contact named above, Geri Redican-Bigott, Assistant Director; Katherine L. Amoroso; Zhi Boon; Sandra George; Alison Goetsch; Cathleen Hamann; Rebecca Hendrickson; Richard Lipinski; Yesook Merrill; Vikki Porter; Oliver Richard; Daniel Ries; Merrile Sing; Alison Smith; and Eric Wedum made key contributions to this report.

# Related GAO Products

*Controlled Substances: DEA Needs to Better Manage Its Quota Process and Improve Coordination with FDA.* GAO-15-494T. Washington, D.C.: May 5, 2015.

*High-Risk Series: An Update.* GAO-15-290. Washington, D.C.: February 2015.

*Drug Shortages: Better Management of the Quota Process for Controlled Substances Needed; Coordination between DEA and FDA Should Be Improved.* GAO-15-202. Washington, D.C.: February 2, 2015.

*Drug Shortages: Threat to Public Health Persists, Despite Actions to Help Maintain Product Availability.* GAO-14-339T. Washington, D.C.: February 10, 2014.

*Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability.* GAO-14-194. Washington, D.C.: February 10, 2014.

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

*Drug Shortages: FDA's Ability to Respond Should Be Strengthened*. GAO-12-116. Washington, D.C.: November 21, 2011.