



441 G St. N.W.
Washington, DC 20548

March 19, 2014

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Mr. Chairman:

Following the February 10, 2014, hearing held by the Subcommittee on Health, *Examining Drug Shortages and Recent Efforts to Address Them*, we received questions for the record from you and other members. This correspondence provides our responses to these questions. If you or your staff have any questions or need additional information, please contact me at 202-512-7114 or crossem@gao.gov.

Sincerely yours,

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

Marcia Crosse
Director, Health Care

Enclosure

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Enclosure

GAO Responses to Additional Questions for the Record

The Honorable Joseph R. Pitts

- 1. The FDA noted that you utilized different data in your study than the data the FDA uses to track drug shortages. Please explain why the different data does not detract from your study and findings.**

As discussed below, the use of data from the University of Utah Drug Information Service (UUDIS) does not detract from our findings and provided the only available data to conduct trend analyses. Although the specific numbers we report, based on our analysis of UUDIS data, differ from FDA's data, the overall trends we report are very similar to those reported by the agency.

To review the trends in recent drug shortages, we analyzed UUDIS data on drugs that were in short supply from January 1, 2007, through June 30, 2013. These data are generally regarded as the most comprehensive and reliable source of drug shortage information for the time period we reviewed and are what we used in preparing our 2011 report.¹ We used UUDIS data because FDA was unable to provide data on shortages that would allow for an analysis of trends for this time frame. As we have previously reported, until FDA established a database containing shortage information in 2011, the agency did not systematically maintain data on shortages.² As we noted in our 2011 report, according to FDA officials, the best data that FDA could then provide to analyze trends would be copies of weekly e-mail messages containing brief narratives on the status of shortages in effect for the week in question. In the absence of FDA data, the data from UUDIS was the only data that we could identify that would allow for a meaningful analysis of drug shortages over time.

Both FDA's analysis in its calendar year 2013 drug shortages annual report and our analysis of UUDIS data show that new drug shortages increased each year from 2007 to 2011 and began to decrease in 2012. While FDA did not report numbers of ongoing shortages in its annual report, its drug shortages strategic plan notes that because shortages typically continue for extended amounts of time, the actual number of shortages at a given point in time is likely to be higher than the number of new drug shortages reported in a given year. This is consistent with our finding that the total number of shortages active during a given year—including both new shortages reported and ongoing shortages that began in a prior year—has increased steadily since 2007.

¹See GAO, *Drug Shortages: FDA's Ability to Respond Should be Strengthened*, GAO-12-116 (Washington, D.C.: Nov. 21, 2011), 2.

²See GAO-12-116.

The Honorable Henry A. Waxman

I understand that GAO analyzed drug shortage data compiled and maintained by the University of Utah Drug Information Service (UUDIS). The year-by-year drug shortage data reported by GAO differ somewhat from those reported by FDA. In order to better understand the significance of the differences, and in particular, how the differences may affect our understanding of the public health impacts of drug shortages, please answer the following questions.

- 1. Does the UUDIS shortage list include shortages that may present temporary problems for pharmacies that do not significantly affect the ability of patients to get access to the drugs they need? Does the FDA shortage list include such local shortages?**

The UUDIS list does not include temporary local shortages, according to a UUDIS official, nor does FDA's list.

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. This definition does not include temporary back orders and supply issues. FDA defines a shortage as occurring when the total supply of a drug and any pharmaceutical equivalents is inadequate to meet demand.³ Upon notification of a potential shortage, both UUDIS and FDA officials told us that they contact all manufacturers of a given drug to investigate supply issues. FDA is also able to compare manufacturer inventory levels to industry sales data on historical demand for the product.

Though FDA's definition of a shortage differs from UUDIS's, the trends we report using UUDIS data are very similar to those reported by FDA. Both FDA's analysis in its calendar year 2013 drug shortages annual report and our analysis of UUDIS data show that new drug shortages increased each year from 2007 to 2011 and began to decrease in 2012. While FDA did not report numbers of ongoing shortages in its annual report, its drug shortages strategic plan notes that because shortages typically continue for extended amounts of time, the actual number of shortages at a given point in time is likely to be higher than the number of new drug shortages reported in a given year. This is consistent with our finding that the total number of shortages active during a given year—including both new shortages reported and ongoing shortages that began in a prior year—has increased steadily since 2007.

- 2. Can the UUDIS shortage list distinguish between shortages of medically important drugs (i.e. - those that are life-saving, life-sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition) and shortages of other drugs? What are the criteria by which a drug shortage is classified as critical? Can a shortage of a non-medically-important drug be listed as a critical shortage? Can a local shortage be listed as a critical shortage?**

According to both UUDIS and FDA officials, neither UUDIS's nor FDA's drug shortages list distinguish between shortages of medically important drugs and other drugs. UUDIS broadly

³A pharmaceutical equivalent is a drug product that is identical in dosage form, active pharmaceutical ingredient (API), and strength, and delivers an identical amount of API over an identical dosing period. See 21 C.F.R. § 320.1(c) (2013).

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. It is important to note that our analysis using UUDIS data focuses on shortages of prescription drugs. We therefore excluded shortages of over-the-counter drugs, biologics (including vaccines), medical devices, and orally-administered vitamins from our analysis, even though UUDIS also tracks these shortages. FDA defines a shortage as occurring when the total supply of a drug and any pharmaceutical equivalents is inadequate to meet demand.⁴ According to FDA officials, the agency tracks all shortages about which it is notified, and posts all verified shortages on its website, not just shortages of medically necessary products.

A subset of the total number of shortages tracked by UUDIS are those shortages identified as “critical,” which UUDIS classifies as such because alternative medications were unavailable, the shortages affected multiple manufacturers, or it received multiple reports from different institutions. According to a UUDIS official, UUDIS data do not distinguish between shortages of medically necessary drugs and other drugs, whether critical shortages or not. Further, UUDIS does not track local shortages, so a local shortage would not be listed as a critical shortage.

3. What is the basis by which a drug is removed from the shortage list? For example, do all the National Drug Code versions of a particular drug have to be restored by a manufacturer before the drug is removed from the shortage list? Will a drug remain on the drug shortage list if the drug is available from other manufacturers?

UUDIS and FDA take a different approach in considering shortages to be resolved and removing such shortages from their respective lists. Once UUDIS identifies a shortage, it generally does not consider a shortage to be resolved until all national drug codes (NDC) are available; that is, generally until the drug is available again in all strengths and package sizes from all manufacturers that currently produce the drug.⁵ 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 Manufacturer 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 informing UUDIS that Manufacturers B and C have increased supply and all market need has been met. According to a UUDIS official, tracking all NDCs for all manufacturers is important for providers because substituting one strength or package size for another may create a safety issue.

FDA considers a shortage to be resolved when the total supply of a drug and any pharmaceutical equivalents is adequate to meet demand. Therefore, if FDA determines that total supply of alternative strengths and package sizes or from alternative manufacturers is

⁴A pharmaceutical equivalent is a drug product that is identical in dosage form, active pharmaceutical ingredient (API), and strength, and delivers an identical amount of API over an identical dosing period. See 21 C.F.R. § 320.1(c) (2013).

⁵An NDC is a unique identifier, although one drug can have multiple NDCs associated with it. For example, a drug made by one manufacturer, in one strength, but in three package sizes would have a different NDC for each of the three package sizes.

adequate, the agency may consider a shortage to be resolved, even if some NDCs or products from some manufacturers are unavailable.

4. Does the UUDIS data enable GAO to distinguish between shortages that have been significantly mitigated and those for which there has been little or no mitigation? If not, would such distinction be useful in determining the relative effectiveness of efforts by FDA and industry to address shortages?

For some shortages, UUDIS maintains information on changes in availability for specific strengths, package sizes, and manufacturers, which could provide some information about the extent to which certain shortages have been mitigated. For all shortages, UUDIS's database tracks the drug name, dates of the shortage, a drug classification code, the cause of the shortage, and whether or not the drug is an injectable. For shortages UUDIS considers critical, it collects additional data, such as estimated resupply dates and the NDCs associated with the shortage, which are publically posted in drug shortage bulletins.⁶ UUDIS regularly updates these bulletins with information about changes in availability of individual NDCs and of products from individual manufacturers.

We have not conducted the work necessary to comment on whether distinguishing between shortages that have been significantly mitigated and those for which there has been little or no mitigation would be useful in determining the relative effectiveness of efforts by FDA and industry to address shortages.

⁶ UUDIS creates a drug shortage bulletin for all shortages that it identifies as critical. Each bulletin is publically posted on the American Society of Health-System Pharmacists' website.

The Honorable Michael C. Burgess

1. In GAO-14-194, the GAO states that “there are shortcomings in its [FDA] management of drug shortage data that are inconsistent with internal control standards.” Would you elaborate on the shortcomings you referenced?

We identified shortcomings stemming from a lack of policies and procedures for managing and using information from FDA’s drug shortage database.⁷ While FDA is planning on establishing a new information system to track drug shortage data, it lacks policies, procedures, and specific training materials related to management and use of its existing drug shortage database. While FDA did create a database glossary, which briefly defines a number of the data fields, an official told us that no other documents or training materials have been created because staff use the existing database every day and are therefore familiar with its operation. Further, while FDA officials said they plan to create policies for entering data in the planned new drug shortage information system and create a tutorial for users, they had not done so as of February 2014. This lack of documentation may limit the agency’s ability to communicate proper use of the existing and new databases to staff and could also ultimately lead to inconsistencies in the use of the database. The lack of policies and procedures is also inconsistent with internal control standards for the federal government, which state that agencies should have controls over information processes, including procedures and standards to ensure the completeness and accuracy of processed data.⁸ For example, internal controls require the appropriate documentation of system controls and that such documents be readily available for review. Such documentation may include management directives, administrative policies, and operating manuals; none of which had been prepared for the existing database as of February 2014.⁹

We also identified shortcomings related to FDA’s lack of policy and procedures for its existing drug shortage database and found that FDA lacks sufficient controls to ensure the quality of the data in the database. For example, FDA officials said there are no automated data checks to ensure the accuracy of the data in the database. Instead, officials review the data for accuracy at the end of each year by relying on their memories of events, emails, and meeting notes. The first such data check was completed in 2012. Officials said they planned to perform another such review at the end of 2013, in preparation for its annual report on drug shortages to Congress. This practice is inconsistent with the internal control standards for the federal government that require agencies to design controls, which may include data checks that help ensure completeness, accuracy, and validity of database entries.¹⁰ Without such data checks, FDA’s existing database may be more likely to have errors, incomplete data, and inconsistent data. We asked officials to provide us with any documentation of their 2012 review of the existing database for accuracy and they were unable to do so. FDA officials said they plan to incorporate automated data checks in their new information system, which may eliminate the need for subsequent manual quality checking. FDA officials told us that, as of January 2014,

⁷GAO, *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability*, GAO-14-194 (Washington, D.C.: Feb. 10, 2014).

⁸GAO, *Standards for Internal Control in the Federal Government*, GAO/AIMD-00-21.3.1 (Washington, D.C.: November 1999).

⁹GAO/AIMD-00-21.3.1.

¹⁰GAO/AIMD-00-21.3.1.

any new drug shortages will be entered into their new information system. Both the lack of adequate policies and procedures governing the use of its database and the lack of sufficient checks to ensure the data's reliability could hinder FDA's efforts to understand the causes of shortages as well as undermine its efforts to prevent them from occurring.

Finally, another shortcoming we identified relates to the fact that FDA has not conducted routine analyses of its existing drug shortage database to identify, evaluate, and respond to the risks of drug shortages proactively. According to the internal control standards for the federal government, agencies should comprehensively identify risk through qualitative and quantitative methods, including data collected in the course of their work. FDA's drug shortages strategic plan states that the agency will explore risk-based approaches to identify early warning signs of problems that could lead to production disruptions. However, FDA currently uses data on an ad hoc basis to respond to specific shortages as opposed to using the data to identify trends or patterns that may help it predict and possibly prevent shortages. According to FDA officials, other than producing the annual report required by the Food and Drug Administration Safety and Innovation Act (FDASIA), the agency has not established regular schedules for generating reports in the database and is not currently using the database to conduct regular trend analyses. By only using the database to respond to individual shortages as they occur, FDA is missing opportunities to use the data proactively to enhance the agency's ability to prevent and mitigate drug shortages. As a result, FDA may be missing an opportunity to identify causes of shortages, risks for shortages, and patterns in events which may be early indicators of shortages for certain types of manufacturers, drugs, or therapeutic classes.

The Honorable Renee Ellmers

- 1. Section 1001 of the FDA Safety and Innovation Act require manufacturers to notify the Agency in instances when the manufacturer discontinues the production of a drug or if an interruption in drug production occurs. This provision of the law also empowers the Agency to issue a failure to notify letter if a manufacturer fails to comply. My understanding is that manufacturers are in good compliance with this notification in FDASIA. Is that correct? Has the Agency been forced to use their failure to notify letter authority in statute?**

We have not conducted work to assess whether manufacturers are complying with the FDASIA requirement that they notify FDA at least 6 months prior to the date of a discontinuance or interruption (or as soon as practicable if 6 months notice is not feasible) in the manufacture of a drug that is life supporting, life sustaining, or used to prevent or treat debilitating health issues when such discontinuance or interruption is likely to lead to a meaningful disruption in supply in the United States. However, FDA officials noted that there has been a sizeable increase in such notifications from manufacturers with a six-fold increase after issuance of the drug shortages Executive Order in October 2011, a subsequent doubling of that rate after the enactment of FDASIA in July 2012, and a return to the post-Executive Order notification rate in 2013.¹¹ As such, in June 2013 FDA officials told us that, at that time, they had not had to consider sending noncompliance letters. Further, FDA is required to provide Congress with an annual report that contains a variety of information related to drug shortages, including a list of manufacturers that were issued noncompliance letters related to the notification requirement. In its annual report for calendar year 2013, FDA notes that, as of February 5, 2014, the agency had issued no such letters. Finally, as of March 11, 2014, no manufacturer noncompliance letters have been posted to the agency's website, as called for in FDASIA.

¹¹On October 31, 2011, the President issued an Executive Order that directed FDA to use its authority to encourage manufacturers to report drug supply disruptions earlier, among other things. Exec. Order No. 13,588 reprinted at 3 C.F.R. 281 (2012).

GAO Responses to Member Requests for the Record

The Honorable John D. Dingell

- 1. Please submit a detailed response regarding how FDA could use its drug shortage database more proactively and whether the Agency needs more resources to implement the recommendations.**

We believe that FDA could use its drug shortages data more proactively by routinely analyzing the data it collects, and that doing so may enhance the agency's ability to prevent and mitigate drug shortages. The agency took an important step in 2011 by creating a database on drug shortages. However, collecting information is not enough. We believe it is important for FDA to maximize the agency's ability to use the information at its disposal. Such an approach is consistent with internal control standards for the federal government, which call for agencies to comprehensively identify risk through qualitative and quantitative methods, including data collected in the course of their work.¹²

Although FDA's drug shortages strategic plan states that the agency will explore risk-based approaches to identify early warning signs of problems that could lead to production disruptions, that had not yet occurred as of February 2014. According to FDA officials, other than producing the annual report required by FDASIA, the agency has not established regular schedules for generating reports in the database and is not currently using the database to conduct regular trend analyses. A routine analysis—rather than an ad hoc approach—could enhance the agency's ability to understand trends in the shortages that are occurring. For example, FDA may be able to study its data and identify trends in the causes of shortages, risks for shortages, and patterns in events which may be early indicators of shortages for certain types of manufacturers, drugs, or therapeutic classes. Not only would this provide the agency with critical information, it could inform its key decisions when faced with a potential or impending shortage. Without such analyses, FDA's ability to manage risk-based decisions, including when to use regulatory discretion, and proactively help prevent and resolve shortages may be hindered.

We did not conduct the work necessary to determine whether FDA currently needs more resources to implement the recommendations in our February 2014 report. However, FDA increased the number of drug shortage personnel from four in 2011 to eleven in 2013, consistent with a recommendation we made in 2011.¹³ FDA officials have said this has improved the agency's ability to respond to drug shortages. Although we have not reassessed FDA's resources devoted to drug shortages, in its comments on a draft of our report, HHS agreed with our recommendation to enhance its oversight by conducting periodic analyses of its drug shortages database.

¹²GAO, *Standards for Internal Control in the Federal Government*, GAO/AIMD-00-21.3.1 (Washington, D.C.: November 1999).

¹³See GAO, *Drug Shortages: FDA's Ability to Respond Should be Strengthened*, GAO-12-116 (Washington, D.C.: Nov. 21, 2011), 43.

The Honorable Brett Guthrie

1. Please provide more detail about FDA's regulatory actions to prevent or mitigate drug shortages based on your discussions with Agency staff as well as manufacturers. Are FDA's actions or decisions being exercised consistently?

FDA has taken a number of actions that have prevented or mitigated drug shortages, including expediting review of abbreviated new drug applications (ANDA) and ANDA supplements, expediting inspections associated with such applications and supplements, and using its regulatory discretion to allow certain products to remain on the market or bring new products to market. According to FDA, between January 1, 2011, and June 30, 2013, the agency expedited 161 ANDAs, 97 ANDA supplements, and 38 new drug application supplements in response to drug shortages. FDA reported that expedited review helped to prevent 211 potential shortages and helped to resolve 27 shortages.

We have not conducted work to determine how consistently FDA has expedited such applications and supplements. However, we spoke to manufacturer representatives who noted that in some cases expedited reviews or inspections have happened quickly and have helped prevent shortages. But others told us that some application reviews or inspections have taken a long time, limiting the manufacturers' ability to help prevent or resolve a shortage. For example, one manufacturer representative said waiting for FDA's approval of ANDA supplements related to new raw material suppliers has been a key hindrance to the manufacturer's ability to respond to drug shortages.

In addition to expediting applications, supplements, and associated inspections to address shortages, FDA officials said that in appropriate cases, the agency may attempt to use its regulatory discretion to keep products from going into short supply or from making an active shortage worse. In these instances, FDA may refrain from taking regulatory or enforcement action to stop the distribution of a drug that is in shortage if the manufacturer makes the decision to continue marketing the drug despite a labeling or quality issue, effectively allowing the manufacturer to continue marketing the drug. In doing so, FDA balances the drug's risk to a patient with the risks of the drug not being available. In one instance, the manufacturer of a drug that may slow the progress of the human immunodeficiency virus and acquired immune deficiency syndrome lost its component supplier and was forced to find a new one. However, this new supplier was experiencing a quality problem. FDA used its regulatory discretion to allow the manufacturer to use the new component supplier while quality problems were being addressed after it determined those issues posed no significant risks to public health. In another instance, FDA used its regulatory discretion to allow the continued marketing of a drug, despite a manufacturing deviation, after determining the benefits of having the drug available outweighed the risk associated with the manufacturing deviation.

In the event that a shortage cannot be averted, FDA may take other actions to enhance product availability. For example, in certain circumstances, FDA may not object to the temporary importation of drugs not approved by FDA for marketing in the United States, subject to appropriate controls, effectively allowing the drugs to be temporarily marketed in the United States. FDA officials said they use their regulatory discretion to temporarily allow the importation of "unapproved drugs" into the United States to help prevent or resolve shortages of FDA-approved drugs that are critical to patients, in rare cases where the shortages cannot be resolved by manufacturers willing and able to supply the FDA-approved drugs in the immediate

future.¹⁴ We previously reported that FDA had allowed for the importation of seven unapproved drugs from January 2011 through September 2011. FDA officials told us that, through June 30, 2013, they have subsequently allowed for the importation of nine additional unapproved drugs.¹⁵ For example, when the manufacturer of a drug used to treat patients who require total parenteral nutrition lost the use of a manufacturing site, FDA allowed importation of a comparable version of the drug not approved by FDA to prevent a potential shortage from occurring.¹⁶

As with the consistency of expediting agency actions, we have not conducted work to determine whether FDA is considering the use of regulatory discretion in a consistent manner. However, several stakeholders told us that FDA's efforts to allow the importation of unapproved drugs to address a shortage have helped to resolve some critical shortages. Other stakeholders noted that certain shortages could not be resolved quickly because it took a long time for FDA to respond to providers' requests to allow importation. For example, some stakeholders noted that delays in the importation of total parenteral nutrition products created significant challenges for treating patients who depend upon them. To help speed up the process of temporary importation, FDA officials said that since January 2012 they have proactively identified foreign manufacturers that have expressed a willingness to import their drugs to help with a shortage. Officials said this has allowed them to reach out to companies more quickly and has already helped the agency address one shortage.

Finally, it is important to note that FDA officials told us that they are currently working on updating the section of the agency's Manual of Policies and Procedures that relates to drug shortage management, including expediting inspections and using regulatory discretion. Additionally, another section of this manual, last revised in April 2012, provides direction for how the agency is to consider and respond to requests for expedited reviews of ANDA supplements, such as for requests that relate to drug shortages.

¹⁴Federal law directs FDA to review samples of drugs being imported into the United States from facilities that are not registered with the agency, and, if it identifies any such drugs as unapproved, to refuse entry of the drug into the country. 21 U.S.C. § 381(a). By not objecting to the entry of certain unapproved drugs to address a shortage, FDA effectively allows the importation and distribution of such drugs, but only under specified, controlled circumstances, and only after review of the manufacturer. FDA officials told us it is evaluating the potential impact of a recent decision issued by the U.S. Court of Appeals for the District of Columbia enjoining FDA from effectively allowing importation of an unapproved drug used by some states to administer a lethal injection on its management of drug shortages. In deference to law enforcement agencies, FDA had not objected to the drug being imported for use in lethal injections. See *Cook v. FDA*, 733 F.3d 1 (D.C. Cir. 2013).

¹⁵According to FDA, the agency attempted to use this strategy in seven other instances, but could not do so. In four instances, FDA could not find a manufacturer willing and able to import the product into the United States to address the shortage. In the other three instances, FDA identified a manufacturer, but the shortage was already being resolved and importation was no longer necessary.

¹⁶Total parenteral nutrition products—including protein, minerals, and vitamins—are administered intravenously to patients who cannot eat or absorb nutrients through other methods.