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EXAMINING DRUG SHORTAGES AND RECENT EFFORTS TO ADDRESS THEM

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRTEENTH CONGRESS

SECOND SESSION

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EXAMINING DRUG SHORTAGES AND RECENT EFFORTS TO ADDRESS THEM

MONDAY, FEBRUARY 10, 2014

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 2:00 p.m., in room 2123, Rayburn House Office Building, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Shimkus, Blackburn, Guthrie, Griffith, Ellmers, Pallone, Dingell, Barrow, and Christensen.

Staff present: Clay Alspach, Chief Counsel, Health; Gary Andres, Staff Director; Sean Bonyun, Communications Director; Matt Bravo, Professional Staff Member; Noelle Clemente, Press Secretary; Paul Edattel, Professional Staff Member, Health; Sydne Harwick, Legislative Clerk; Carly McWilliams, Professional Staff Member, Health; Katie Novaria, Professional Staff Member, Health; Heidi Stirrup, Health Policy Coordinator; John Stone, Counsel, Health; Josh Trent, Professional Staff Member, Health; Tom Wilbur, Digital Media Advisor; Ziky Ababiya, Democratic Staff Assistant; and Eric Flamm, Democratic FDA Detailee.

Mr. PITTS. The subcommittee will come to order. The Chair will recognize himself for an opening statement.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

In recent years, we have seen a dramatic increase in the number of drug shortages in the United States, particularly with generic sterile injectable drugs. While the number of new shortages dipped in 2012 and 2013, the total number of ongoing shortages has continued to increase. This is unacceptable. Numerous drugs have remained on FDA's shortage list for some time. What is the Agency doing to help address these situations?

Recent news reports have highlighted shortages of oncology products, parenteral nutrition products and even common, yet critically important, saline solutions. Such shortages lead to delays in treatment, rationing of care and higher costs. They can also pose greater risks to patients in the form of medication errors and as providers are forced to seek alternative treatments. Drug shortages are a very challenging problem and it is clear that there is no sim-

ple solution. We recognize the complicated nature of this issue as well as the severity.

Last Congress, the subcommittee took action by including a section on drug shortages in the Food and Drug Administration Safety and Innovation Act, FDASIA, which was signed into law on July 9th, 2012. Title 10 of FDASIA sought to address drug shortages by giving new authorities and responsibilities to the Food and Drug Administration and placing expanded requirements on drug manufacturers to notify FDA of an interruption or discontinuance in production. Among other provisions, under FDASIA, the Secretary of Health & Human Services is required to, one, maintain a publicly available up-to-date drug shortage list; two, establish a task force to implement a strategic plan to prevent and mitigate drug shortages; and three, submit annual reports to Congress, including relating actions taken by the Agency. FDASIA also required GAO to examine the cause of drug shortages and formulate recommendations on how to prevent or alleviate drug shortages.

Last October, FDA issued its strategic plan for preventing and mitigating drug shortages. Further, we now have FDA's first annual report on drug shortages, though it only covers the first three quarters of 2013. And today, GAO released its final report pursuant to FDASIA.

While drug shortages continue to plague our health care system, statistics do indicate progress on some fronts. I am pleased to see that legislation coming out of this subcommittee has had a positive impact.

I would like to welcome our witnesses, Marcia Crosse, health care director at GAO, and Douglas Throckmorton, deputy director of regulatory programs at the FDA.

I would particularly like to thank GAO for their comprehensive report and the time they have spent with my staff on this issue.

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

In recent years, we have seen a dramatic increase in the number of drug shortages in the United States, particularly with generic sterile injectable drugs.

While the number of new shortages dipped in 2012 and 2013, the total number of ongoing shortages has continued to increase. This is unacceptable. Numerous drugs have remained on FDA's shortage list for some time. What is the agency doing to help address these situations?

Recent news reports have highlighted shortages of oncology products, parenteral nutrition products, and even common, yet critically important saline solutions.

Such shortages lead to delays in treatment, rationing of care, and higher costs. They can also pose greater risk to patients in the form of medication errors and as providers are forced to seek alternative treatments.

Drug shortages are a very challenging problem and it is clear that there is no simple solution. We recognize the complicated nature of this issue as well as the severity. Last Congress, the subcommittee took action by including a section on drug shortages in the Food and Drug Administration Safety and Innovation Act (FDASIA), which was signed into law on July 9, 2012.

Title X of FDASIA sought to address drug shortages by giving new authorities and responsibilities to the Food and Drug Administration and placing expanded requirements on drug manufacturers to notify FDA of an interruption or discontinuance in production.

Among other provisions, under FDASIA, the Secretary of Health & Human Services is required to: (1) maintain a publicly available, up-to-date drug shortage list; (2) establish a task force to implement a strategic plan to prevent and mitigatedrug

shortages; and (3) submit annual reports to Congress including relating actions taken by the agency.

FDASIA also required GAO to "examine the cause of drug shortages and formulate recommendations on how to prevent or alleviate such shortages."

Last October, FDA issued its "Strategic Plan for Preventing and Mitigating Drug Shortages." Further, we now have FDA's first annual report on drug shortages, though it only covers the first three quarters of 2013.

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Mr. PITTS. I will yield the remainder of my time to Vice Chair Dr. Burgess.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Mr. Chairman.

You know, when doctors don't have the essential tools, they are restricted in what they can do for their patients. Members of this committee have taken the lead and made major strides in working to reduce drug shortages by passing the Food and Drug Administration Safety and Innovation Act of 2012. In addition, I have worked very closely with Chairman Upton and Chairman Pitts on several of the provisions contained therein, and things have gotten better, but the problems have not completely gone away.

As recently as last week, the Food and Drug Administration listed sodium chloride injection bags as a drug shortage. Now, sodium chloride is not a particularly esoteric or exotic molecule, so if we are having that much trouble with salt, it only makes you wonder what other more difficult molecules may—the shortages that we may encounter there.

The Food and Drug Administration has a role in addressing drug shortages, but it is a complex issue. In 2010, over 240 drugs were in short supply or unavailable, and more than 400 generic equivalents were back ordered. In fact, many generic lines operate at margins so tight, that when production becomes corrupted, the company simply cannot afford to continue its manufacture. This inevitably leads to one of the more than 3,000 backlogs of generic applications.

Physicians are still faced with having to tell patients that they can't receive the care they need, not because there is no treatment but because a product is simply not available.

I thank the chairman for holding this hearing so we can learn more about the progress that is being made on the Nation's drug shortage problem. I am pleased that the Government Accountability Office report is being released and look forward to hearing from them on their findings. The law is aimed to ensure that providers have the tools they need to alleviate suffering, the suffering of every patient, and certainly, I am anxious to hear the testimony today.

I yield back to the chairman.

Mr. PITTS. The Chair thanks the gentleman.

Now yields 5 minutes for opening statement to Mr. Pallone.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairman Pitts. I am glad we are having the hearing today on this critical issue of drug shortages.

Over the past several years, we saw an alarming trend of increases in drug shortages, and we all know the devastating effects this can have on patients, potentially prolonging disease or causing permanent disability or even death. This is an issue I and many of my colleagues on the committee have long been concerned about. Congress took action to provide the Food and Drug Administration with tools to help address this problem through provisions in the Food and Drug Administration Safety and Innovation Act, or FDASIA, which passed on a strong bipartisan basis in the summer of 2012.

In FDASIA, we asked the Government Accountability Office to review several factors related to drug shortages, updating work it had done previously, and they released that report today. And I am glad Dr. Crosse is here to discuss it further with us.

I also want to take a moment to highlight some of the other aspects of FDASIA that addressed the drug shortage problem. In its 2012 report on drug shortages, the GAO recommended and we heard this from other stakeholders, too, an early notification requirement for potential shortages so that FDA can work with manufacturers sooner to take steps to prevent or mitigate shortages. We included such a requirement in FDASIA, and it is encouraging that the number of new drug shortages declined in 2012 compared to the previous 2 years and that partial data from 2013 indicates that the trend is continuing.

The FDA has cited this and other FDASIA drug shortage provisions as contributing to their ability to prevent, by their calculation, 140 drug shortages in the first three quarters of 2013.

We also heard from stakeholders the need for faster review times for generic drug applications and to reduce the significant backlog of pending applications, and the generic user fee agreement that was passed as parts of FDASIA was important in getting FDA the resources it needs to make that happen.

We have learned that it can be important to have multiple manufacturers, especially for the most medically important drugs, to help alleviate drug shortages. As we heard from FDA a few months ago, the Agency has been aggressively hiring FTEs for its generic drug program, meeting hiring goals in the law as part of its efforts to tackle the backlog and speed up review times.

And these are just some of the steps that have been taken to address drug shortages, which is, of course, a complex problem. As I am sure we will hear today from our witnesses, drug shortages remain high and remain a problem. Many of the shortages are still of sterile injectable drugs, and I am aware that these types of drugs face unique challenges, because they are technically difficult to manufacture. And each drug is often manufactured by one or a small number of companies, making it difficult for other companies

to be able to fill the need if any one company develops manufacturing problems.

So it is clear that while we have made progress in some areas, our work is not over. I thank our witnesses from FDA and GAO for being here today to continue our discussion on the topic of drug shortages, and I look forward to learning more about what we can do to further prevent them. Thank you very much.

Thank you, Mr. Chairman. I yield back.

Mr. PITTS. At this time, the Chair recognizes the vice chair of the committee, the gentlelady from Tennessee, Mrs. Blackburn, for 5 minutes for opening statement.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Mrs. BLACKBURN. Thank you, Mr. Chairman.

And I want to welcome our witnesses. I thank you all for being here. And I thank the chairman and the vice chairman of the committee for their attention to this issue.

As you all know, 2011, 2012, we held hearings, we have looked at this process and what the factors are that are causing the drug shortages, and we know that they have increased in recent years. And I am one of those I believe let's get to the root cause and to the root problem so that we are solving this. And I continue to talk with those health professionals in the community in Tennessee and get their input on this.

We did take a bipartisan action, as the chairman and the ranking member have mentioned, and that was to address through FDASIA the shortages. And FDASIA did provide FDA with the authority that they needed. It put new requirements on the manufacturers to help prevent and to mitigate the shortages, or supposedly, on paper, that is what they are to do.

So this is a wonderful opportunity for us to look at the GAO report, to question you, to hear from you and to continue to try to look at this systemically, holistically and to get to the root causes of solving this problem.

And, Mr. Chairman, I yield back to you for further yielding.

Mr. PITTS. The Chair thanks the gentlelady. That concludes the panel's—or members' opening statements.

On the panel today, we have two witnesses: Dr. Marcia Crosse, Director of Health Care, U.S. Government Accountability Office, and Dr. Doug Throckmorton, Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

Thank you for coming. Your written testimony will be made part of the record. You will have 5 minutes to summarize your opening statement.

And at this time, the Chair recognizes Dr. Crosse for 5 minutes for her summary.

STATEMENTS OF MARCIA CROSSE, DIRECTOR, HEALTH CARE, GOVERNMENT ACCOUNTABILITY OFFICE, AND DOUGLAS C. THROCKMORTON, DEPUTY DIRECTOR OF REGULATORY PROGRAMS, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH & HUMAN SERVICES

STATEMENT OF MARCIA CROSSE

Ms. CROSSE. Chairman Pitts, Ranking Member Pallone and members of the subcommittee, I am pleased to be here today to discuss our work on drug shortages.

As you know, prescription drugs are a critical part of medical care, but over the last decade, there has been an increase in the number of drugs that are in shortage. This has included drugs to stabilize trauma victims, to control pain during surgery, to treat heart disease and cancer, and to provide nutritional support to premature infants.

Today, GAO released our report on drug shortages, a study you mandated in the FDA Safety and Innovation Act, and I am happy to discuss our key findings. We found that the number of drug shortages remains high and that providers experience challenges responding to shortages without adversely affecting patient care. Beginning in 2007, the number of new drug shortages increased each year until 2012, when the number of new shortages declined, and that downward trend appears to have continued through 2013, based on the partial year data we analyzed.

However, while the number of new drug shortages has begun to decline, the total number of shortages active during a given year, including both new shortages and ongoing shortages that began in a prior year, has continued to increase, because many shortages are prolonged, with some spanning multiple years. The majority of shortages are of sterile injectable drugs, particularly generics.

Shortages of medically necessary drugs can have a range of negative effects. A drug shortage may require providers to delay or ration care, create difficulties finding alternative drugs, increase the risk of medication errors, lead to higher costs, reduce time for patient care, and result in the hoarding or stockpiling of drugs in shortage. For example, providers may have to ration care by prioritizing the patients who have a greater need for the drug.

The immediate cause of a drug shortage can generally be traced to a manufacturer halting or slowing production to address quality problems, triggering a supply disruption. Other manufacturers have a limited ability to respond to supply disruptions due to constrained manufacturing capacity.

We also identified potential underlying causes specific to the economics of the generic sterile injectable drug market, such as that low profit margins have limited infrastructure investments or led some manufacturers to exit the market. Although there are few studies of underlying causes, among the issues that have been examined are that purchasers focus primarily on price rather than quality, reducing incentives for manufacturers to invest in maintenance or quality improvements; that group purchasing organizations negotiate reduced drug prices on behalf of hospitals and other providers, lowering profit margins for manufacturers that win con-

tracts and leading losing manufacturers to exit the market; and that a 2005 change in Medicare Part B drug reimbursement policy for outpatient providers decreased both demand and prices for generic drugs.

The stakeholders we met with, which included manufacturers and group purchasing organizations, had mixed views on these potential underlying causes, with no general agreement on the role such factors may play.

In examining FDA activities, we found that the Agency has prevented more potential shortages and improved its ability to respond to shortages in the last 2 years. The new requirement that manufacturers must notify FDA in advance of a potential shortage has allowed FDA to take steps to prevent and mitigate shortages sooner. For example, it has expedited application reviews and inspections, exercised enforcement discretion, and helped manufacturers respond to quality problems.

These steps are important to respond to some of the immediate causes of shortages. However, some of the underlying causes we identified are beyond the Agency's authority, as FDA does not have control over private companies' business decisions. For example, the Agency is unable to require manufacturers to start producing or continue producing drugs or to build redundant manufacturing capacity, regardless of the severity of a shortage.

Nonetheless, FDA can take steps to maximize the Agency's use of the information it has to address drug shortages. We identified shortcomings in its management and use of the Agency's drug shortage data. In our report, we made recommendations to FDA to improve its database and to conduct routine analyses, and the Agency has agreed with these recommendations.

In summary, while FDA has made progress in preventing potential drug shortages and responding to actual shortages, the number of shortages remains high and many persist for months and even years. The large number of potential shortages reported to the Agency suggests the market is still at risk of supply disruptions. As a result, patients and providers will continue to struggle as essential and life-saving medications remain in short supply.

Mr. Chairman, this completes my prepared statement, and I would be happy to respond to any questions you or other members of the subcommittee may have.

Mr. PITTS. Thank you.

[The prepared statement of Ms. Crosse follows:]

United States Government Accountability Office

Testimony

Before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives

For Release on Delivery
Expected at 2:00 p.m. EST
Monday, February 10, 2014

DRUG SHORTAGES

Threat to Public Health Persists, Despite Actions to Help Maintain Product Availability

Statement of Marcia Crosse
Director, Health Care

GAO-14-339T

GAO Highlights

Highlights of GAO-14-339T, a testimony before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives

February 10, 2014

DRUG SHORTAGES

Threat to Public Health Persists, Despite Actions to Help Maintain Product Availability

Why GAO Did This Study

From prolonged duration of a disease, to permanent injury, to death, drug shortages have led to harmful patient outcomes. FDA—an agency within the Department of Health and Human Services (HHS)—works to prevent, alleviate, and resolve shortages. In 2011, GAO recommended that FDA should enhance its ability to respond to shortages. In 2012, the Food and Drug Administration Safety and Innovation Act (FDASIA) gave FDA new authorities to address drug shortages. FDASIA also mandated GAO to study drug shortages.

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

What GAO Recommends

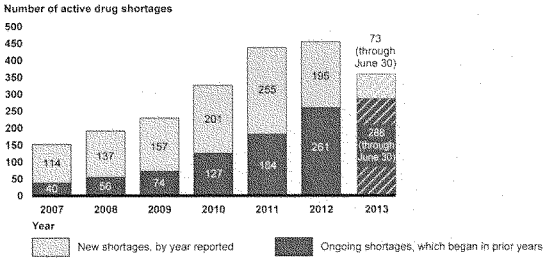
GAO recommended that FDA strengthen internal controls over its drug shortage data and conduct periodic analyses to routinely and systematically assess drug shortage information, using this information to proactively identify drug shortage risk factors. HHS agreed with GAO's recommendations.

View GAO-14-339T. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

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

Number of Active Drug Shortages from January 2007 through June 2013



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

The immediate cause of drug shortages can generally be traced to a manufacturer halting or slowing production to address quality problems, triggering a supply disruption. Other manufacturers have a limited ability to respond to supply disruptions due to constrained manufacturing capacity. GAO also identified potential underlying causes specific to the economics of the generic sterile injectable drug market, including that low profit margins have limited infrastructure investments or led some manufacturers to exit the market.

While shortages have persisted, the Food and Drug Administration (FDA) has prevented more potential shortages in the last 2 years by improving its responsiveness. FDA has initiated steps to improve its response to shortages, such as modifying the information on its drug shortages website. However, there are shortcomings in its management of drug shortage data that are inconsistent with federal internal control standards. For example, FDA has not created policies or procedures governing the management of the data and has not conducted routine analyses using these data. Such shortcomings could ultimately hinder FDA's efforts to understand the causes of specific shortages as well as undermine its efforts to prevent them from occurring.

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee:

We are pleased to be here today to discuss our work on drug shortages. Drug shortages have led to harmful outcomes for patients of all ages: from prolonged duration of a disease, to permanent injury, to death. Over the last decade, an increasing number of prescription drugs have been in short supply. The Food and Drug Administration (FDA)—an agency within the Department of Health and Human Services (HHS)—is responsible for overseeing the safety and effectiveness of drugs marketed in the United States, including by addressing drug shortages.[1] A unit within FDA, referred to as the Drug Shortage Staff (DSS), coordinates the agency's activities to prevent, alleviate, and resolve shortages. In November 2011, we found that the agency lacked sufficient authority to respond to shortages. We recommended that FDA strengthen its response and suggested that Congress consider establishing a requirement for manufacturers to report potential or actual supply disruptions to FDA.[2] The Food and Drug Administration Safety and Innovation Act (FDASIA), enacted in July 2012, provided FDA new authorities to address drug shortages and assigned the agency new responsibilities.[3] It also mandated us to update our work on drug shortages. This statement summarizes the findings in our report, being released today, entitled *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability*.[4]

As part of its oversight of drugs, FDA's approval is required before new drugs and generic drugs can be marketed for sale and its responsibilities continue once a drug is approved for marketing.[5] If FDA identifies a violation of law or regulations, it may issue a warning letter or take an enforcement action. In some cases, FDA may exercise its regulatory

[1]FDA defines a drug shortage as a situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand.

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

[3]Pub. L. No. 112-144, 126 Stat. 993 (2012).

[4]GAO-14-194 (Washington, D.C.: Feb. 10, 2014).

[5]21 U.S.C. § 355.

discretion and assess whether the risks of taking a certain enforcement or other action will outweigh the benefits; for example, when an action may cause or exacerbate a drug shortage, FDA may exercise its regulatory discretion and refrain from taking action.[6]

When FDA is informed of a potential shortage in advance, it may take steps to prevent the shortage, such as providing assistance to the manufacturer to address manufacturing problems.[7] For example, it may offer feedback on a manufacturer's proposed approach to responding to quality concerns. In addition, FDA can expedite the review of a drug application or can expedite inspections once remediation to address quality problems has been completed.[8] While there are a number of steps FDA can take to address a shortage, FDA cannot require manufacturers to start producing or continue producing 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.

FDASIA required us to examine several different aspects of shortages. Our report, and my remarks today, focus on 1) the trends in recent drug shortages and describes what is known about their effect on patients and providers, 2) the causes of drug shortages, and 3) the progress FDA has made in addressing drug shortages.[9] To address these issues, we analyzed data from the University of Utah Drug Information Service (UUDIS) on drugs that were in short supply from January 1, 2007,

[6]In determining how to respond to a shortage, FDA takes steps to assess whether a drug is medically necessary, defined as any drug that is used to treat or prevent a serious disease or medical condition for which there is no other adequately available drug that is judged by medical staff to be an appropriate substitute.

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

[8]FDA periodically inspects drug manufacturing establishments to assess their ongoing compliance with Current Good Manufacturing Practice regulations. These regulations provide a framework for a manufacturer to follow to produce safe, pure, and high-quality drugs. See 21 C.F.R. pts. 210-211.

[9]Our report also describes steps federal agencies have taken to respond to gray market activities and describes incentives that have been proposed to prevent shortages. GAO-14-194.

through June 30, 2013.[10] We interviewed representatives from 10 national associations representing health care providers—including physicians, hospitals, and pharmacists—and from eight drug manufacturers and associations representing them, and reviewed relevant documents from these groups.[11] We performed a search of research databases to identify literature on the causes of drug shortages, and analyzed FDA data on the reported causes of shortages that occurred from January 1, 2011, through June 30, 2013.[12] We reviewed documentation and interviewed FDA officials regarding the agency's current approach to managing drug shortages and implementing FDASIA requirements, and compared this approach to the relevant standards described in the *Standards for Internal Control in the Federal Government* and to the agency's requirements under FDASIA.[13] Our work was performed in accordance with generally accepted government auditing standards.

We found that the number of drug shortages remains high and that providers experience challenges responding to drug shortages without adversely affecting patient care. From 2007 through 2011, the number of drug shortages reported increased each year, with a record 255 shortages reported in 2011.[14] However, in 2012, 195 shortages were reported; this was the first decrease from one year to the next since 2006.

[10]These data are generally regarded as the most comprehensive and reliable source of drug shortage information for the time period we reviewed. We reviewed all UUDIS data used for reasonableness, outliers, and consistency; based on our review, we determined that the data were sufficiently reliable for our purposes.

[11]We interviewed three leading national associations representing drug manufacturers, both brand-name and generic, and five generic sterile injectable manufacturers. Specifically, we selected the top three manufacturers of generic sterile injectables between 2010 and 2012. We also selected two additional manufacturers, which were among the manufacturers associated with the highest number of shortages, according to the following report: IMS Institute for Healthcare Informatics, *Drug Shortages: A Closer Look at Products, Suppliers, and Volume Volatility*. (Parsippany, N.J.: November 2011).

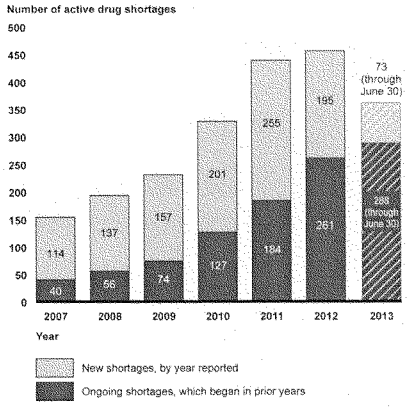
[12]We reviewed all FDA data used for reasonableness, outliers, and consistency; based on our review, we determined that the data were sufficiently reliable for our purposes.

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

[14]A shortage is only counted in the total for "reported" shortages in the year that UUDIS is first notified of the shortage. For example, a shortage reported in July 2010 and resolved in March 2012 would only be counted as a reported shortage in 2010. It would not be counted as a reported shortage in either 2011 or 2012, although it would be counted in the total number of active shortages in each of those years.

Though the number of newly reported shortages has recently declined, due to ongoing shortages that began in prior years, the number of active shortages has increased steadily since 2007 and remains high.[15] The number of active shortages each year almost tripled between 2007 and 2012 from 154 in 2007 to 456 in 2012 (see fig. 1).

Figure 1: Number of Active Drug Shortages from January 2007 through June 2013



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

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

We found that many shortages involved generic sterile injectable drugs. Specifically, based on our review of the characteristics of a subset of critical drug shortages, we found that 44 percent of the 219 critical

[15]The active shortage total for each year includes both (1) new shortages reported that year and (2) shortages that started in a prior year that were still ongoing. For example, a shortage reported in July 2010 and resolved in March 2012 would be counted as an active shortage in three different years (2010, 2011, and 2012).

shortages involved generic sterile injectable drugs.[16] Further, four therapeutic classes—anti-infective, anesthetic and central nervous system, cardiovascular, and nutritive—comprised 53 percent of critical drug shortages.[17]

Faced with this continuing problem, provider association representatives identified challenges in responding to drug shortages without adversely affecting patient care. Provider association representatives told us that a number of the challenges that we reported in 2011 were still relevant for their members. Providers may be challenged by delays in or rationing of care, difficulties finding alternative drugs, risk associated with medication errors, higher costs, and reduced time for patient care.

We also found that quality problems resulting in supply disruptions and constrained manufacturing capacity were frequently cited as the immediate causes of recent drug shortages. We determined that the most frequently cited immediate cause of a drug shortage was when a manufacturer halted or slowed production after a quality problem was identified, resulting in a supply disruption.[18] These supply disruptions were linked to, among other things, such problems as bacterial contamination or the presence of glass or metal particles in drug vials. Although quality problems were a frequently cited issue, there was not complete agreement as to whether quality problems were always the primary trigger for the supply disruptions that cause shortages, with two studies and three manufacturers suggesting that changes in FDA inspections of manufacturing establishments also played a role. In

[16]UUDIS identified 219 of the 382 shortages reported from June 1, 2011, through June 30, 2013, as critical shortages. We reviewed the characteristics of those 219 critical shortages, which represented 57 percent of all shortages reported during this time. These shortages were identified by UUDIS as critical because alternative medicines were not available, the shortages affected multiple manufacturers, or it received multiple reports from different institutions.

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

[18]As shortages have been concentrated in the generic sterile injectable market in recent years, the literature on the subject of shortages and comments from manufacturer representatives largely focused on the causes of shortages specific to that market. As a result, our discussion about the causes of shortages may not be applicable to all shortages.

reviewing the literature, we identified a number of additional factors that can cause supply disruptions and ultimately result in shortages—such as permanent product discontinuations or the unavailability of raw materials—but our analysis of FDA data and interviews with representatives of drug manufacturers suggested that these factors play a relatively small role overall.

Constrained manufacturing capacity limits other manufacturers' ability to respond to supply disruptions. There are few generic sterile injectable manufacturers overall, and the existing manufacturers are producing a large number of drugs. For a variety of reasons, these manufacturers have little flexibility to increase production in existing facilities or move production to alternative facilities.

In addition, half of the studies we reviewed suggested that the immediate causes of drug shortages, such as quality problems, are driven by an underlying cause that stems from the economics of the generic sterile injectable drug market. However, the studies that cited underlying causes did not all focus on the same underlying cause. The potential underlying causes cited in the literature were that competition in the generic drug market focuses primarily on price; the possible role of group purchasing organizations; and a change in Medicare Part B reimbursement policy. The studies that cited these underlying causes generally suggested that such causes led to low profit margins, which limited infrastructure investments or led some manufacturers to exit the market. Manufacturer representatives had mixed views on the potential underlying causes we identified in the literature.

Finally, we determined that FDA has prevented more potential shortages and improved its ability to respond to shortages since we issued our prior report on this topic in 2011. Based on our analysis of FDA data from January 2011 through June 2013, FDA was able to prevent 89 potential shortages in 2011, 154 potential shortages in 2012, and 50 potential shortages through June 2013.[19] This is more than the 35 potential

[19]As we did in analyzing data for our 2011 report, we grouped together shortages of multiple versions of the same drug to identify the total number of potential shortages prevented. While FDA had reported preventing 195 potential shortages in 2011, 282 potential shortages in 2012, and 80 potential shortages through June 2013, we found that these data represented the number of individual drug products for which a shortage had been averted.

shortages we found that FDA prevented in 2010 and the 50 prevented through June 2011.

FDA officials told us that FDASIA's requirement that manufacturers notify FDA in advance of a potential shortage allowed FDA to employ various steps to prevent or resolve shortages sooner.[20] Such steps include expediting a number of agency actions to prevent or resolve shortages, contacting manufacturers regarding their ability to increase production, and facilitating the availability of drugs from alternate sources to help prevent or resolve a shortage. FDA has taken steps to further enhance its ability to respond to shortages, such as modifying the information the agency displays on its drug shortages website, developing a drug shortage database, and increasing the number of DSS personnel from 4 in 2011 to 11 in 2013.

While FDA is planning on establishing a new information system to track drug shortage data, we found that it still lacks policies, procedures, and specific training materials related to management and use of its existing drug shortage database. 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.[21] In addition, we found 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. Again, according to the internal control standards for the federal government, agencies should comprehensively identify risk through qualitative and quantitative methods, including data collected in

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

[21]GAO/AIMD-00-21.3.1.

the course of their work.[22] We determined that 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. 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.

Based on our work, we have identified two actions that we recommend the Commissioner of FDA take to enhance its oversight of drug shortages:

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

In commenting on a draft of our report HHS agreed with our recommendations and stated that it will continue improving the collection of drug shortage data as part of a larger system that would help identify problems with quality drug manufacturing as they evolve. HHS also stated that it agrees that policies and procedures for drug shortage data entry are important and noted that FDA has ongoing work to ensure such policies and procedures are established.

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee, this concludes my prepared remarks. I would be pleased to respond to any questions you may have.

[22]GAO/AIMD-00-21.3.1.

For future contacts regarding this statement, please contact Marcia Crosse ((202) 512-7114 or crossem@gao.gov). Individuals making key contributions to this testimony and the report on which it is based include Geri Redican-Bigott, Assistant Director; Katherine L. Amoroso; Alison Goetsch; and Eagan Kemp.

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Mr. PITTS. The Chair now recognizes Dr. Throckmorton, 5 minutes to summarize his opening statement.

STATEMENT OF DOUGLAS C. THROCKMORTON

Mr. THROCKMORTON. Mr. Chairman and members of the subcommittee, I am Douglas Throckmorton, Deputy Director of FDA's Center for Drug Evaluation and Research. Thank you for the opportunity to speak with you today about the work FDA is doing to address drug shortages.

I would like to begin by discussing their causes. Drug shortages, as others have said, are usually preceded by a disruption in manufacturing of a product. Some product disruptions are manufacturer controlled, such as decisions to permanently discontinue production of a drug that is no longer profitable. Other factors are outside the manufacturer's control, such as natural disasters or the unavailability of materials needed for manufacturing, a particular problem when materials are only available from one supplier.

Most often, however, shortages are the result of quality failures within manufacturing facilities, such as failing to follow proper sterilization procedures that allow bacteria to grow in a sterile product. Quality failures can also result from failures to maintain a manufacturing line: For example, poorly maintained, old equipment has led to the introduction of iron particulates in injectable products. Preventing these supply disruptions requires the manufacturer to commit to quality manufacturing.

Turning to drug shortages in the U.S. today, while work remains, progress has been made in the prevention and resolution of drug shortages in the United States. The Agency is well positioned to work with manufacturers to find ways to prevent or reduce a shortage's impact on patients, provided we are aware that there is the potential for a shortage. Early and timely notification by manufacturers has been aided importantly by the Executive Order of the President as well as by passage of FDASIA and has enabled FDA and manufacturers to prevent 170 shortages in 2013.

We are also seeing fewer new shortages. The number of new drug shortages in the United States rose steadily from 60 in 2005 to an all-time high in 2011 of 251 new shortages. After a series of interventions, the number of new drug shortages has fallen to a low of 44 in 2013.

There do, however, continue to be shortages that persist for longer periods. Here, while progress is being made, the FDA is tracking and working to resolve 97 total shortages that began in 2013 or earlier. This work has been accomplished by FDA working closely with manufacturers, and some of the tools we have applied include identifying manufacturers who are willing and able to increase production of a drug in shortage; expediting FDA inspections and reviews of submissions, both from manufacturers that are currently producing as well as manufacturers who are interested in starting new production of a drug in shortage; and, finally, exploring risk mitigation measures for products initially not meeting established standards to allow them to remain available safely.

While FDA's standards of safety, efficacy and quality do not change in a shortage situation, FDA does balance our standards with the needs of patients for particular products, especially pa-

tients with limited treatment options. FDA makes certain that drug shortages are considered before taking enforcement actions or issuing warning letters. In appropriate cases, temporary exercise of regulatory flexibility is an important tool in ensuring access to needed drugs.

As a part of FDA's work on drug shortages in 2013, the FDA released its strategic plan, as called for in FDASIA. The goals of the plan are to improve the Agency's response to drug shortages and to advance longer-term approaches for addressing the underlying causes of shortage.

First, to improve how we address imminent or existing shortages, FDA is focusing on three areas: First, we are improving communications within CDER within the FDA to ensure that our decisions are efficient and appropriate. Second, we are improving our databases related to drug shortages, creating a dedicated drug shortage data system to improve how we track drug shortages and allow us to better assess progress on prevention and mitigation of those shortages, including the work we do to produce the annual report to Congress required under FDASIA. Third, FDA continues to work to improve timely and accurate communication about drug shortages to patients and caregivers.

Recognizing that drug shortages commonly begin with the supply disruption related to product quality, FDA's long-range efforts include a focus on preventing supply disruptions and shortages by encouraging and sustaining improvements in manufacturing quality. For over a decade, FDA has been working with academics and industry experts to stimulate the development of novel manufacturing technologies which can help prevent drug shortages linked to manufacturing quality.

In conclusion, progress has been made in efforts to prevent and mitigate important drug shortages, aided by early communications with sponsors about potential shortages. Shortages do continue to occur. FDA will continue to work to address them. Importantly, FDA will continue to work with others to support the pharmaceutical industry in their long-term efforts to modernize drug manufacturing to prevent shortages. By working together, we can prevent drug shortages from occurring, address them when they do occur, and provide patients with access to medicines when they are in critical need.

I am happy to answer any questions that you have.

Mr. PITTS. The Chair thanks the gentleman.

[The prepared statement of Mr. Throckmorton follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

"EXAMINING DRUG SHORTAGES AND RECENT EFFORTS TO ADDRESS THEM"

February 10, 2014

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Douglas Throckmorton, Deputy Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to speak with you today about the progress FDA has made in preventing and mitigating drug shortages.

Drug shortages pose a significant public health threat, affecting individual patients from across the United States, including patients who are in need of drugs to treat life-threatening diseases such as cancer, serious infections, and malnutrition. Recently, for example, there have been reported stock shortages of normal saline, a critical fluid used in the treatment of shock. These shortages can result in delaying or denying needed care to patients and may lead practitioners to prescribe an alternative therapy that may be less effective for the patient or that poses greater risk. Shortages have occurred, impacting care delivered by care providers in our Emergency Medical Services and in our emergency departments. Drug shortages have even disrupted clinical trials, potentially delaying research on important new therapies.

The number of new drug shortages in the United States rose steadily between 2005, when FDA began tracking 60 new shortages and the all-time high in 2011, when 251 new shortages were reported. After a series of interventions, including a Presidential Executive Order, enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA outreach, and work with the pharmaceutical community, the number of new drug shortages declined significantly in 2012 to 117 and fell even further to 44 in 2013. However, there continue to be

shortages that persist for longer periods, and currently, FDA is tracking 97 total shortages that began in 2013 or earlier.

Preventing drug shortages has been, and continues to be, a top priority for FDA. Recognizing the importance of this issue, we have increased substantially the resources we devote to drug shortages and expanded our work to prevent them. While the Agency cannot solve the problem alone, working in partnership with manufacturers and other stakeholders, and within the confines of the current statutory and regulatory framework, FDA helped prevent 170 shortages in 2013, 282 shortages in 2012, and 195 shortages in 2011. FDA has also identified future actions that can help prevent shortages, including important work to support new manufacturing methods that promise high-quality drug manufacturing, that would help to ensure patients have needed access to lifesaving medicines and help revitalize pharmaceutical manufacturing in the United States. In my testimony, I'd like to share with the Committee some of the work FDA is doing, and the plans the Agency has to continue to work to address this important public health issue.

Causes of Drug Shortages in the United States Today

Addressing the issue of drug shortages first requires an understanding of the causes of drug shortages. While increases in demand for a given drug can sometimes challenge the drug supply, drug shortages are usually preceded by a production disruption, which can be either a permanent product discontinuation or temporary interruption in manufacturing. Once a manufacturer experiences a discontinuance or interruption in manufacturing, a shortage may occur if there is no other manufacturer to step in to fill the gap in supply, or if other manufacturers cannot increase production quickly enough to make up the loss.

These production disruptions can be triggered by several factors, including factors within the control of manufacturers, such as a decision to permanently discontinue production of a drug because the product is no longer profitable. Production disruptions can also be caused by factors outside of the manufacturer's control, such as natural disasters or the unavailability of raw materials or needed materials for drug manufacturing. For example, shortages have resulted when raw material manufacturers discontinue the production of a needed ingredient for business reasons. In these circumstances, manufacturers relying on the ingredient may be unable to locate and qualify a new supplier in time to avoid a shortage. This is a particular vulnerability, if the ingredient is only available from one supplier (so-called 'sole-source').

FDA has had to intervene in the past to prevent shortages resulting from problems with non-U.S.-based suppliers. For example, shortages have resulted when raw material manufacturers discontinue an ingredient for business reasons. As noted above, manufacturers relying on the ingredient may be unable to locate and qualify a new supplier in time to avoid a shortage. Examples of critical drugs currently or recently in shortage with an active ingredient and/or finished goods sourced primarily from overseas include propofol, heparin, and Tamiflu. In some instances, our reliance on non-U.S.-sourced materials affect response to public health vulnerabilities.

Most often, however, production disruptions leading to shortages are the result of failures within manufacturing facilities that result in failures of product or facility quality. These quality failures include failing to follow proper operator procedures on sterile lines, allowing the growth

of bacteria and fungus. Moreover, just like an older car, aging production lines and the facilities that house them require significantly more upkeep. For example, poorly maintained old equipment has led to the introduction of steel and iron particulates into injectable products. Addressing these quality problems can result in a supply disruption that can result in a drug shortage. In 2012, for example, based on information collected from manufacturers, FDA determined that 66 percent of production disruptions leading to a shortage resulted from either (1) efforts to address product-specific quality problems (31 percent) or (2) efforts to address broader problems at a manufacturing facility (35 percent). As discussed below, preventing these disruptions requires a commitment on the part of the manufacturer to quality manufacturing, putting in place controlled production that ensures consistent drug quality. When these systems fail, a production can be disrupted and a firm may initiate a recall that leads to a shortage. In such cases, FDA can work with firms to remediate quality issues while production continues, however, some firms have taken the unilateral decision to shut down operations.

Responding to Drug Shortages

While manufacturers have a central role in ensuring that drugs are manufactured to a consistently high quality, FDA and other stakeholders have important roles to play in addressing drug shortages in the United States. When FDA is aware of an imminent or ongoing shortage, the Agency is well-positioned to work with the affected manufacturer to find ways to prevent or mitigate the shortage and lessen a shortage's impact on patients. The numbers are worth repeating: with early and timely notification by manufacturers, FDA helped prevent 170 shortages in 2013, 282 shortages in 2012, and 195 shortages in 2011. These numbers illustrate the value of FDA's receiving early notification of potential drug shortages. Several recent actions have supported such early notification. First, President Obama issued Executive Order 13588, "Reducing Prescription Drug Shortages," on October 31, 2011, which immediately

strengthened the Agency's response to shortages by directing FDA to use all appropriate administrative tools to improve manufacturers' notifications of potential shortages. In response, FDA issued an interim final rule to require early notification from certain manufacturers. In addition, on July 9, 2012, the Congress provided FDA with new authorities as part of FDASIA. Section 1001 of FDASIA broadened the scope of the early notification provisions by requiring all manufacturers of all covered prescription drugs (approved or unapproved) to notify FDA of a permanent discontinuance or temporary interruption in manufacturing. FDASIA also allowed FDA to require, by regulation, early notification of discontinuances or interruptions in the manufacturing of biologic products. In response to these actions, in October 2013, FDA issued a proposed rule. The proposed rule would implement the new reporting requirements, and would also extend these requirements to manufacturers of medically important biologic products. FDA is currently reviewing the comments on the proposed rule.

Since the Executive Order was issued in October 2011, FDA has seen a six-fold increase in the number of notifications from manufacturers (from 10 notifications per month prior to the Executive Order to an average of 60 per month since the Executive Order). FDA also learns about potential shortages from a variety of sources outside of the drug manufacturer—including professional organizations, interest groups, patients, and health care professionals—who report shortage information to multiple FDA offices. This work, coordinated through the Drug Shortage Staff, is included in the data we use when assessing a potential shortage, and helps ensure that FDA is aware of the shortages and their potential impact as early as possible.

FDA's staff has a variety of tools to help prevent or mitigate shortages. FDA staff, led by the Drug Shortage Staff, begins by verifying that an actual shortage exists or may occur. When the

shortage staff determines that a shortage either exists or is likely to occur, shortage staff members lead and coordinate the mitigation efforts with multiple other offices within FDA. Working with FDA's drug review division and/or professional organizations, they determine if the drug is medically necessary. FDA uses the information about whether or not a drug is medically necessary to prioritize its response to a shortage overall and to inform the risk-benefit assessment for the specific product in question.

FDA can and does take a variety of actions to mitigate or prevent shortages:

- Identify the extent of the shortfall and determine if other manufacturers are willing and able to increase production to make up the gap
- Expedite FDA inspections and reviews of submissions from manufacturers attempting to restore production
- Expedite FDA inspections and reviews of submissions from competing manufacturers who are interested in starting new production or increasing existing production of products in shortage
- Exercise temporary enforcement discretion for new sources of medically necessary drugs
- Work with the manufacturer to ensure adequate investigation into the root cause of the quality problem
- Explore risk-mitigation measures for products initially not meeting established standards to allow them to be used safely.

The decisions FDA makes regarding a given drug shortage take into account both the risks and the benefits of continuing to make a drug available for patients. While FDA's standards of safety, efficacy, and quality do not change in a shortage situation, the benefits and risks of providing patients access to the specific product are always considered as the Agency determines what the best approach is for a given shortage. Our goal is to ensure that an adequate supply of approved drugs for all patient needs is available. However, FDA recognizes that there may also be risks to patients when treatment options are not available for critical conditions and understands the importance of using the appropriate tools to prevent or mitigate a shortage. FDA also makes certain that drug shortages are considered before taking an enforcement action or issuing a Warning Letter. In appropriate cases, temporary exercise of regulatory flexibility has proven to be an important tool in ensuring access to treatment options for health care practitioners and patients in critical need.

We also expect that an increase in availability of generic drugs on the market can help mitigate future drug shortages. Generic drug user fee resources, including those recently made available through the Generic Drugs User Fee Amendments of 2012 (GDUFA), can speed access to safe and effective generic drugs to the public.

Continuing FDA Progress on Drug Shortages: the FDA Strategic Plan

Responding to notifications about potential shortages has enabled FDA, working with other groups, to prevent a significant number of drug shortages. Going forward, there is important additional work to do to reduce the factors that lead to shortages. In October 2013, the Agency released a Strategic Plan ("the Plan"), called for in FDASIA, both to improve the Agency's

response to imminent or existing shortages and to advance longer-term approaches for addressing the underlying causes of shortages to prevent supply disruptions from occurring in the first place. The Plan also recognizes the important role of other groups in preventing drug shortages and highlights opportunities for drug manufacturers and others to prevent drug shortages by promoting and sustaining quality manufacturing. This Plan was created by a Task Force representing multiple Centers, Offices, and disciplines from across FDA—a group that continues to work to implement the actions identified in the Plan.

First, FDA is working to strengthen FDA's ability to respond to a notification of a production disruption to prevent a shortage or to mitigate an unavoidable shortage by improving the processes we use to respond to shortages. We are working to continue to improve communications within FDA to ensure that our decisions are made as efficiently as possible. Second, recognizing the importance of up-to-date and accurate data, we are also working on ways to improve our databases related to drug shortages as well as the tracking procedures we use to manage those databases. This is a complex task, as some of these data systems that support efforts to prevent shortages were not created specifically for the purposes of assisting shortage-related activities. As a result, in addition to these more general data systems, the Agency is creating a dedicated data system that focuses solely on collecting data related to shortages—a system that will be able to integrate data from the other general data systems. This new drug data system will enable FDA to more efficiently track and assess issues relating to drug mitigating shortages, including enhancing our tracking of time from notification of shortage to resolution. The new system also will enhance FDA's ability to compile the information necessary for the required annual report to Congress on drug shortages. Third, FDA understands the importance of timely and accurate information about shortages for patients and caregivers

who are concerned about the availability of a particular drug, and the Agency continues to work to improve our communications about drug shortages.

The Future—Developing Long-Term Prevention Strategies

In addition to the activities FDA is taking to address current drug shortages, our Strategic Plan also addresses the development of long-term strategies focused on the underlying causes of production disruptions. While keeping in mind the critical role other stakeholders play in ensuring manufacturing quality, FDA is also exploring actions it can take, both alone and in collaboration with other groups, to address the issue of manufacturing quality.

FDA is exploring how we can use the tools we have to help support manufacturing quality through our own actions. We are also continuing to work with other stakeholders to understand and identify potential warning signals that could put the production of quality drugs at a given facility at risk. Early identification of these signals could allow for actions by the manufacturer to prevent shortages. Identifying these signals is a challenging undertaking, and FDA will work with a wide variety of stakeholders, who have collected and analyzed data about drug shortages and potential approaches to predict the risk for shortage, earlier.

FDA also recognizes that other proposals to reduce the risk of drug shortages would rely on actions by other stakeholders. Opportunities for others to explore could include better planning to prepare for potential manufacturing disruptions; the use of economic, financial, or other incentives for innovation and new investments in manufacturing quality drugs to reduce the occurrence and severity of shortages; and efforts to address concerns about the impact of

secondary distribution of approved drug products in shortage that can lead to higher prices (so-called 'Gray Market' activities).

The Future—Manufacturing Modernization and Shortage Prevention

Recognizing that shortages commonly begin with a supply disruption related to product or facility quality, FDA's efforts include a focus on encouraging and sustaining improvements in manufacturing quality. For over a decade, FDA has been working with academic and industry experts to stimulate development of novel manufacturing technologies with a goal of supporting these needed improvements. This work has supported advances in pharmaceutical manufacturing technology in the last decade that provide new opportunities to address the primary drivers of drug shortages and, potentially, to reinvigorate the pharmaceutical manufacturing sector in the United States. This work has included guidance and other actions to encourage manufacturers to adopt new manufacturing technologies, to facilitate their use of modern quality management techniques, and to ensure that FDA regulatory policies reflect state-of-the-art manufacturing science. Importantly, these efforts by FDA have focused on the need to encourage the adoption of new technologies and do not impact the standards for existing appropriate technologies or raise the bar on their use.

FDA is actively encouraging development of techniques that can help advance drug manufacturing. One example of a technique that holds promise is "continuous manufacturing," wherein the finished drug product is produced in a continuous manufacturing process, as opposed to traditional methods that involve a series of so-called "unit operations," such as milling, mixing, and granulation. Production can be continuous from chemical synthesis of the active ingredient through production of the tablets or other dosage form, which can support

better control of product quality and can make changes in product, such as scale-up, easier to accomplish.

CONCLUSION

Drug shortages remain a significant public health issue in the United States, and addressing them is a top priority for the Agency. By working closely with manufacturers experiencing problems, as well as potential alternative manufacturers, and by exercising regulatory flexibility in appropriate cases, FDA has had a substantial positive impact on the shortage situation. Although the number of new shortages decreased in 2012 and 2013, and FDA has been able to prevent many shortages, nearly 100 drugs were in active shortages as of December 31, 2013. Many of the remaining drugs in shortage have been in ongoing shortage for the past several years because manufacturers have been unable to address the issues that led to the shortage or have chosen not to continue their availability. FDA will continue to work with manufacturers and other stakeholders to search for new tools to address these long-term shortages. However, an examination of the sources of drug shortages underscores the fact that FDA cannot do this alone and reinforces the importance of strong collaboration and constant communication between FDA, industry, health professionals, and patients. Because the majority of drug shortages begin with quality manufacturing problems, supporting sustained investment in reliable, high-quality modern drug manufacturing is an important target for future work. FDA has been working for over a decade, in collaboration with the pharmaceutical industry, to modernize drug manufacturing. These activities, combined with the other important work by FDA and other stakeholders, hold the key to preventing drug shortages from occurring, addressing them when they do occur, and providing patients with access to medicines they need.

I am happy to answer any questions you may have.

Mr. PITTS. That concludes the opening statements of the panel. We will now begin questioning, and I will recognize myself for that purpose for 5 minutes.

Dr. Throckmorton, while FDASIA required that the report be submitted by no later than December 31st, 2013, FDA's first annual shortages report was submitted to the committee on February the 5th and with data from only the first three quarters of 2013. You notice in your testimony that 170 new shortages were prevented in 2013. This is up from 140 in the report FDA submitted to the Congress. I assume that means that FDA claims to have prevented 30 shortages in the fourth quarter of the year. Is that correct?

Mr. THROCKMORTON. We do have our full-year data available now, and we would be happy to share that with you, Mr. Chairman.

Mr. PITTS. All right. Well, let's use that smaller sample size for sake of discussion. It would be helpful to have more detailed information about how FDA prevented these shortages. What specific actions did the Agency take? Which drug products would currently be in shortage if not for the Agency's actions?

Mr. THROCKMORTON. I can get you some specific information, but I can give you a general sense of some of the activities that we took in this last year, if that would be helpful.

Mr. PITTS. All right.

Mr. THROCKMORTON. One issue regards something called regulatory flexibility. So these are places where we have either expedited additional actions that otherwise would have taken a bit longer or taken a review under hand and done additional work on it. And last year, we had 76 instances of regulatory flexibility that we exercised, affecting a total of 68 products.

There is another way of thinking about the actions that we have taken recently to try to speed the development of products or assure that products that potentially go into shortage remain available; that is by looking at the kinds of expedited reviews that my review staff do. So several of the offices receive applications from sponsors for new factories, for new lines within a factory. Last year, my Office of Generic Drugs expedited 118 applications, involving a total of 62 accelerated new drug applications, so an important number of products where we worked hard to make certain that they were more quickly reviewed than normal. Our Office of New Drug Quality, which is another office looking at supplemental applications to approve drugs, approved innovator drugs, looked at 52 supplemental applications in an expedited forum last year. And then finally, my Office of Biologic Products, which looks at new biologic products, obviously, a very important issue in terms of therapeutics and therapeutic development, they expedited seven reviews last year.

I think, so, in total, those things reflect the kind of commitment that my center has to looking at these things, expediting wherever we are able to devote our resources to do it.

Mr. PITTS. OK. Now, you mentioned the Office of Generic Drugs expedited 118 applications, including 62 abbreviated new drug applications. ANDA, is that what you call it?

Mr. THROCKMORTON. Yes.

Mr. PITTS. In order to prevent or mitigate a shortage, how many of those applications were actually approved?

Mr. THROCKMORTON. You know, I would need to get back with you about that information. Obviously, we are applying our usual standards, but 118 applications, I think, speaks to the level of effort that we undertook.

Mr. PITTS. On average, how long did it take FDA to approve an ANDA that was given expedited review status? Do you know?

Mr. THROCKMORTON. It is a good question, and I will get back with you with that information.

Mr. PITTS. OK. And I would like to know more about what expedited review means in this situation. Does an ANDA referencing a product in shortage go to the top of the queue? Is there a special team within the Office of Generic Drugs responsible for moving them through the review process faster?

Mr. THROCKMORTON. This will be a longer conversation. As I am sure you are aware, we have new resources under GDUFA, under the Generics Drugs User Fee Act. As a part of those resources, we have reorganized the Office of Generic Drugs. We are elevating it in terms of its importance within the Center for Drugs, and as a part of that action, we are looking to be as efficient as we possibly can. So to answer your question, I am going to need to get back and look at the kinds of changes that that office has made about the review staff.

Mr. PITTS. All right.

Dr. Crosse, did you have any discussions with FDA review staff about what it means for a shortage product to receive expedited review status within OGD?

Ms. CROSSE. We did talk with FDA about this. We actually are continuing our work looking at drug shortages where we are planning on taking a more in-depth review of the number of drug shortages that have been expedited and how that relates to the number of applications that are sitting in the queue for drugs that are in shortage. One issue, of course, is that even when you expedite an application, if it is approved, that doesn't mean that the manufacturer is ready to begin production that day. And there is some concern that approving one ANDA may displace another drug within that manufacturer's facility if you are trying to move very quickly to move something to the top of the line without the sort of normal planning time, so that is something we heard about, but we are looking further to try to get some statistics for you on how frequently FDA is moving on these applications and what proportion of the applications are getting moved on.

Mr. PITTS. Yes. And I would also be interested in how FDA works with the manufacturer to address their targets to assess when production capacity and output has addressed the shortage.

My time has expired.

The Chair recognizes the ranking member, Mr. Pallone, 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to start with Dr. Throckmorton. I would like to know how helpful you are finding the drug shortage provisions in FDASIA, and whether there are other things that you think Congress should do to help address drug shortages. And I would also

like to hear more about FDA's strategic plan for preventing and mitigating drug shortages. I was pleased to see that it was released last October, in fulfillment of one of your FDASIA obligations.

So essentially three questions: Would you update us on how things stand today with regard to drug shortages and the Agency's plan to address them? And now that FDA has some experience with FDASIA, are there parts of the law that don't work as intended or, you know, as well as they should? And then, third, are there other areas we should be thinking about to help address the shortages?

Mr. THROCKMORTON. Well, thank you. So, first, let me just say the provision of FDASIA that expanded the notification that manufacturers have been providing for us has been enormously helpful. It is hard for me to overstate that. We are learning about shortages earlier than we had previously, and it is giving us the opportunity to talk with manufacturers in ways that we hadn't had an opportunity before, and we have been able to prevent shortages as a result. So, unquestionably, that aspect of FDASIA has been useful from the FDA's perspective. We continue to make use of it. As you know, we are continuing to write rulemaking and things related to it, but it is fundamentally a valuable aspect of the work that we are doing that is very useful.

The other aspects of FDASIA, I think, have also been useful for us as well. The requirement to produce an annual report, I think, is valuable, because it does give us an opportunity on an annual basis to look back and assess whether there are things that we need to continue to work on or where progress has been made. That is a piece that we were able to provide to you recently for three quarters of the year's data. We, obviously, need to update you with the full-year data, because we think that gives a fuller picture of the activities that the FDA—that the—that FDA has conducted. And so, fundamentally, FDASIA has been valuable to us from a shortage prevention strategy.

Now, you asked us whether additional things were identified in the strategic plan that needed also to be done, and the short answer is yes. So there are many things that we can do internally. There are things that we need to do from a process perspective to make sure that the FDA continues to improve our responses to the drug shortages issue, and that—those relate, many of them, to process. So I chair the task force that has been steering our response to drug shortages since FDASIA's passage. That task force is made up of individuals from across the Agency, so not just simply my center, but also the Center for Biologics, the inspectional branch of the FDA. All of us are coming together to talk about the things we need to do, the things that we need to communicate about better, to be able to, you know, basically do the job more efficiently and more appropriately.

We also recognize we need to improve our communications. The communications we place on the Web site are looked at hundreds of thousands of times by individuals looking for information about shortages. We heard loud and clear when we talked to our stakeholders what needed to be improved, so that the information was easier to find, so that topical information was easier to identify, that the normal saline shortage, for instance, was at the top of the

queue, when you opened up that Web page, that you could get that information quickly. We have heard those kinds of comments, and we are doing what we can to improve those communications.

Separately, however, there are things that are, as Dr. Crosse said, outside of our scope, outside of the things that the FDA is able to undertake. There are things that the manufacturers, we believe, have a role to explore, and there are other things that other stakeholders could explore as well that have great potential, I believe, in addressing the underlying causes of shortage. Happy to talk with you about those if you are interested.

Mr. 1PALLONE. All right. Let me just get into one more question, because my time is almost gone here. One of the GAO's recommendations is that FDA conduct routine analysis of its drug shortage database to identify trends, and that seems like a reasonable suggestion. Seems like FDA already does this to some extent but perhaps not in as formalized a process as the GAO.

Can you just tell us a little more on the problems of the current FDA databases and what you hope the improvements will accomplish, and does FDA believe that performing analysis such as GAO recommends would help it come up with the recommendations for avoiding shortages?

I think you will have 15 minutes—15 seconds.

Mr. THROCKMORTON. Fundamentally, we agree with the recommendations that the GAO has made. We understand that the quality of the decisionmaking that we can have with regards to shortage depends on the quality of the data. So we are putting in place a new drug shortage data system that is going to make the data more robust, make it more standardized and improve our assessment of those data.

Mr. PALLONE. OK. All right. Thanks a lot.

Thanks, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the gentlelady from Tennessee, Mrs. Blackburn, 5 minutes for questions.

Mrs. BLACKBURN. Thank you, Mr. Chairman.

And, again, I thank each of you for being here with us.

I want to—I have got just a couple of questions. I know that the FDA report said, you know, the number of reported new shortages has declined in 2012 and for the first three quarters of 2013, but then GAO says the total number of active shortages continues to be high. So do you each agree with that?

Dr. Crosse?

Ms. CROSSE. Yes, we do agree. The number of new shortages has decreased, and we think that the FDASIA early notification has been very helpful in that regard, but a number of shortages have persisted across time.

Mrs. BLACKBURN. OK.

Ms. CROSSE. I think we present that information in our report.

Mrs. BLACKBURN. Yes, you do.

Dr. Throckmorton, do you continue to—do you agree with that, that the shortages continue to be too high?

Mr. THROCKMORTON. Absolutely. I mean——

Mrs. BLACKBURN. OK. Just want to be sure everybody is in complete agreement on that, because what I am hearing from the providers in Tennessee, they agree with the GAO report.

And, Dr. Throckmorton, they look at yours, and it is kind of a head scratcher, because they are not seeing the amount of improvement that your report would lead people to believe is there. And we continue to hear about the shortages with the generic sterile injectable drugs, the IV fluids, the medications for anesthesia, some of the cancer therapies. So these are problems, and you might be making some progress, but it is not coming fast enough.

And so let's talk about FDA implementing the system and preventing—getting to the point that they can prevent new shortages and decrease the backlog of the current shortages.

So, Ms. Crosse, give me the couple of things that we need to be holding them responsible for doing. What is going to speed this up, because we can't do this where we are saying 10 years from now, we are going to have this in place?

Ms. CROSSE. Well, we do continue to look at some of the underlying causes. You know, I think we need to look a little more closely at those generic drug applications that are sitting at FDA and the extent to which FDA has been able to expedite the applications, which could be something that would help, but——

Mrs. BLACKBURN. OK. Let me.

Ms. CROSSE [continuing]. There are still a number of——

Mrs. BLACKBURN. If I can engage you right there for just a minute.

Ms. CROSSE. Sure.

Mrs. BLACKBURN. So Dr. Throckmorton, you said you expedited 118 this year.

Mr. THROCKMORTON. Generic applications, yes.

Mrs. BLACKBURN. OK.

Dr. Crosse, what would be a better number? What—if you were setting a goal for him, how many should they be expediting every year? Two hundred?

Ms. CROSSE. I don't know.

Mrs. BLACKBURN. You don't know.

Ms. CROSSE. I don't know. And I think there is a concern that if you expedite too many, that then you are creating a clog at the top.

Mrs. BLACKBURN. OK.

Ms. CROSSE. It is difficult. You need—you know, there—even within the priorities——

Mrs. BLACKBURN. Thank you. So——

Ms. CROSSE [continuing]. There are priorities.

Mrs. BLACKBURN [continuing]. It may be approved, but then they can't put it straight into manufacturing.

Ms. CROSSE. Right. So there needs to be conversations with the manufacturers about how quickly they could come on line.

Mrs. BLACKBURN. So they need to be engaging them on the front end rather than the back end——

Ms. CROSSE. Yes.

Mrs. BLACKBURN [continuing]. Or at the point of approval.

Would predictability in this process with the review system, because as I talked to some that are working in the generic space,

the bio-therapeutic space, the unpredictability at the FDA seems to be a problem?

Dr. Crosse, would that help?

Ms. CROSSE. You know, that is not something that we heard from the manufacturers——

Mrs. BLACKBURN. OK.

Ms. CROSSE [continuing]. Particularly. I think that, you know, certainly that is always an issue in any review process for the applications, but it is not something that they particularly pointed to here, because of the unpredictability of when a shortage might occur.

Mrs. BLACKBURN. OK.

Dr. Throckmorton?

Mr. THROCKMORTON. I want to try to draw a distinction between the numbers of ongoing shortages, those that last extended periods of time, which are important—and that is one group of shortages that I think we know less about than we need to, I think that is a group that bears additional exploration—and the numbers of new shortages and the numbers of new shortages prevented. So when I answered your question that there are too many shortages, I—there are too many shortages because they are shortages that impact on human access to drugs in the U.S. I mean, that is—

Mrs. BLACKBURN. Sure.

Mr. THROCKMORTON [continuing]. We would have to do away with those before there would not be too many shortages.

Having said that, however, I think we have to acknowledge that there has been work that has been important, that has been able to prevent new shortages from adding onto that pile, if you were. We are able to prevent shortages that matter. Our next important task, a task that I think we need to undertake, is to understand those longer duration shortages, those shortages that mean no product is in the marketplace at all; there is no manufacturer willing and interested in manufacturing the product.

Mrs. BLACKBURN. My time has expired. I thank you for that additional explanation.

Mr. Chairman, as I yield back to you, I do want to take a moment and wish happy birthday to Congressman Guthrie.

Yield back.

Mr. PITTS. The Chair thanks the gentlelady and, well——

Mr. GUTHRIE. You didn't say which birthday.

Mr. PITTS [continuing]. Wishes Mr. Guthrie a happy birthday.

At this time, the Chair recognizes the ranking member emeritus of the full committee, Mr. Dingell, 5 minutes for questions.

Mr. DINGELL. Mr. Chairman, I thank you for your courtesy and for holding this important hearing. I am pleased the committee is turning again to the important topic of drug shortages. There are many causes for this: the availability of raw materials, complexity of manufacturing, certain treatments, sudden increases in demand. We have also got a significant problem in adequate funding for FDA and an adequate number of personnel to properly address the business of that Agency. While we have made some progress in this area, such as the passage of the FDA Safety and Innovation Act, which improved communication and reporting of drug shortages,

we all agree, I think, that there is more work to be done. So I hope our witnesses will answer the questions yes or no.

Dr. Throckmorton, the last time this committee held a hearing on drug shortages, the situation was dire. Is it correct that the number of new drug shortages quadrupled from 2005 to 2011, yes or no?

Mr. THROCKMORTON. Yes.

Mr. DINGELL. Now, Doctor, is it correct that there are only 44 new drug shortages in 2013 compared with 117 during the year 2012, yes or no?

Mr. THROCKMORTON. Yes.

Mr. DINGELL. Now, Doctor, is it correct that FDA successfully prevented 170 drug shortages in 2013, yes or no?

Mr. THROCKMORTON. Working with manufacturers, yes.

Mr. DINGELL. Now, Dr. Crosse, although GAO used slightly different metrics, did your Agency also find a decrease in new drug shortages during 2012, yes or no?

Ms. CROSSE. Yes.

Mr. DINGELL. Dr. Throckmorton, did the new authorities provided in the—to the Agency in FDASIA help FDA to reduce the number of new drug shortages, yes or no?

Mr. THROCKMORTON. Yes.

Mr. DINGELL. Would you submit for the record additional changes that need to be made to further reduce the delays and the shortages when they occur?

Mr. THROCKMORTON. Yes.

Mr. DINGELL. I also would like to know, would more personnel and more money assist FDA in terms of addressing these questions?

Mr. THROCKMORTON. We are devoting resources we need to this problem.

Mr. DINGELL. And so, Doctor, would you submit us a short monograph on that——

Mr. THROCKMORTON. Yes.

Mr. DINGELL [continuing]. To assist the committee?

Dr. Throckmorton, does FDA need additional authorities to help combat both existing and future drug shortages, yes or no?

Mr. THROCKMORTON. Existing authorities are providing us important tools.

Mr. DINGELL. Would you please submit a detailed response to the record, including the resources needed by the Agency?

Mr. THROCKMORTON. Yes.

Mr. DINGELL. Dr. Crosse, GAO's report on drug shortages makes two recommendations to FDA. Specifically, you recommend that the Agency use its drug shortage database in a more proactive manner to identify trends and patterns to help prevent shortages before they occur. Is that correct?

Ms. CROSSE. Yes.

Mr. DINGELL. Now, Dr. Throckmorton, does FDA agree with this recommendation?

Mr. THROCKMORTON. Yes.

Mr. DINGELL. Would you please both submit a detailed response for the record regarding how FDA could use this database more

proactively and whether you need more resources to implement the recommendations?

Mr. THROCKMORTON. Yes.

Ms. CROSSE. Yes.

Mr. DINGELL. Now, I am pleased with the progress made in preventing drug shortages since the passage of FDASIA. We need to take a step back and look at the big picture. Fundamentally, drugs are in shortage because we simply aren't making enough of them. As you know, many current shortages are of generic sterile injectable drugs.

Dr. Throckmorton, does FDA believe there is sufficient incentives to enter this market today, or are more needed?

Mr. THROCKMORTON. Important question. I can't answer it without a fuller discussion with other stakeholders.

Mr. DINGELL. Would you submit a proper analysis, then, in response to this?

Mr. THROCKMORTON. Yes.

Mr. DINGELL. Now, I think it is time to start thinking outside the box about how we can continue to make progress on preventing these drug shortages and combating existing shortages. We need new and new innovative ideas to help solve the problem as well as cooperation from all stakeholders. I look forward to working with my colleagues on the committee, the FDA and all stakeholders on this critical issue moving forward.

Mr. Chairman, I thank you and I yield back the balance of my time.

Mr. PITTS. The Chair thanks the gentleman.

Now yields 5 minutes to the vice chairman of the subcommittee, Dr. Burgess, for questions.

Mr. BURGESS. Thank you, Mr. Chairman.

Dr. Throckmorton, you know, we had the Executive order from October of 2011 and then, of course, Food and Drug reauthorization in July of 2012, but for the casual observer to this problem of drug shortages, can you kind of just give us a thumbnail of what is being done to deal with the existing drug shortages?

Mr. THROCKMORTON. We have a number of things. First off, I would say existing drug shortages, especially those that have lasted for a prolonged period of time, are hard. They are hard to resolve, because the factors that have led to them have meant manufacturers have left that space entirely, so resolving those is going to require finding tools to encourage a new manufacturer to decide to add a product to a manufacturing line, make a decision that that is a product that they can make a profit at, decide to design that line and get approvals and things. So that—those long-term shortages are things I think we need to explore further than we have to date to now.

Mr. BURGESS. Hold that thought for just a second. Let me just ask you, have the manufacturers been responsive?

Mr. THROCKMORTON. Manufacturers understand this issue. We have been in close discussion with many of the manufacturing organizations, ISPE and PDA and other groups. They have identified this group, these groups of longer-term shortages as things that we need to continue to talk about, absolutely.

Mr. BURGESS. You know, Dr. Crosse talked about enforcement discretion and you talked about exercise of regulatory flexibility. Can you give us some practical examples of where that exercise of regulatory flexibility—I mean, for example, the anesthetic drug propofol, has there been any? Is there anywhere where regulatory flexibility may help in that particular shortage?

Mr. THROCKMORTON. Let me give you a slightly different example, and then we can return to propofol if it isn't useful, but let's talk about total parenteral nutrition, or the nutritional supplements that were in critical shortage recently that are used in newborn infants, where it is just really life or death for them to be able to get access to these medicines.

Those products were in limited availability because the manufacturers are having a hard time producing enough sufficient materials. FDA expedited any and every review, expedited all of our inspectional activities to make certain that whatever the manufacturer was able to provide, we were able to make certain was available to serve the infants, the newborns as quickly as possible.

We have had other examples where particulates have been found, examples of drugs in shortage where particulates have on surface required cessation of manufacture, cessation of distribution of the product. Because of their critical nature, we worked with the manufacturers, we have worked to find filters that could be placed in line when that product is administered to the patient, allowing them to continue to be used. Even though that there is this product defect, these particulates that exist, we have determined they have to be made available to the patients, we have worked with the manufacturers to make that happen. So——

Mr. BURGESS. And so that has been successful. Talk about propofol, though, because I get a lot of questions about that. I mean, lack of an anesthetic, a reliable, safe anesthetic drug is a—I mean, it is a big deal.

Mr. THROCKMORTON. Absolutely. And propofol's a slightly different situation, because there the issue is a large fraction of the propofol comes from outside the U.S. Well over 90 percent of the propofol is imported into the country, and there have been some concerns about importation as—because of some use of propofol in unapproved uses.

The FDA's interest, the focus that we have had, has been to make certain that the propofol is available for patients who are using it on label as indicated, as you said, in outpatient settings for anesthesia and those things. So our work there has been to work with the sponsor to do anything we needed to make sure the patients received it when it was indicated for them; 5 million units, dosages a month or something, it is an enormously important product that we are paying very close attention to.

Mr. BURGESS. Well, and it has revolutionized outpatient surgery because the recovery time is so abbreviated with that as opposed to the other compounds that were previously available in days gone by.

Mr. THROCKMORTON. Absolutely. And we know that when in the past, there was a propofol shortage a few years ago, and what we learned in that shortage was that when physicians moved from propofol to other products that they were less familiar with, you

know, mistakes occurred, because they were not as familiar with the dosage and how to monitor patients and things like that. So making certain that that product is available is something that is very important for the U.S.

Mr. BURGESS. Just very briefly, I have heard anecdotally that difficulties getting proper amounts of Tamiflu during this last flu season and that the cost for Tamiflu had really exponentially increased. Can you speak to that at all?

Mr. THROCKMORTON. I haven't heard that the cost of Tamiflu has spiked. There are other increases in pricing that we have been hearing about, although that is not something that the FDA normally, you know, has the statutory authority over. And while there were some spot shortages with Tamiflu, we think at present we are able to produce the needed—the necessary amounts of Tamiflu necessary.

Mr. BURGESS. Thanks, Mr. Chairman.

I have some additional questions I will submit in writing, but I thank you for the courtesy.

Mr. PITTS. The Chair thanks the gentleman.

Now recognize the gentlelady from Virgin Islands, Dr. Christensen, for 5 minutes for questions.

Ms. CHRISTENSEN. Thanks, Mr. Chairman. And I want to thank you and the ranking member for this hearing today.

While I am very happy to hear that the drug shortages are reducing, as everyone has said, they still remain too high, and we know that rural areas, communities of color, territories like my district will be some of those where we will feel it the most when there is a drug shortage.

I have a question that sort of digs a little deeper into my colleague from Tennessee, the vice chair's question, I think. And I am asking both—I will start with Dr. Throckmorton, but also ask Dr. Crosse to comment. One of the explanations I have heard for the increase in drug shortages was that FDA was forcing manufacturers to come up with the state-of-the-art manufacturing practices, even though the old tried and true were completely adequate to ensure safety and effectiveness. The argument went that to meet the new standards, some companies had to shut down their lines to upgrade their facilities, resulting in the shortages.

I have also heard something that is almost the opposite argument, that FDA had been telling some companies for years that their facilities were in decline and needed to be upgraded to avoid problems in the future, even though the facilities were currently meeting inspection standards, and eventually, those warnings, unfortunately, came through.

So, Dr. Throckmorton, can you comment on these two different perspectives? You mentioned in your testimony that FDA is trying to encourage industry to adopt new technologies but, at the same time, that FDA is not raising the bar, is not raising the bar on standards for existing appropriate technologies. That seems a very nuanced point. Could you just elaborate for me?

Mr. THROCKMORTON. Absolutely. So there are a set of standards that are in place right now for manufacturing, for sort of quality manufacturing that we would expect a firm that is making propofol, a firm that is making a tablet form, whatever, a set of

standards that they have in place that would guide, you know, the manufacture of a product so that it is sufficiently safe and efficacious in quality manufacturing. Those things are working, and we are not changing those standards at all.

What we also see is that there are more efficient ways to be manufacturing products, especially products that are very complicated, products that are like sterile injectables or products that are biologics, places where you want to use the state-of-the-art manufacturing processes. We have been working for over a decade now trying to identify those manufacturing processes to help guide drug manufacturing and then make recommendations in the form of guidance in ways that manufacturers can look at to do better than the current.

So we are not looking to change the current acceptable process practices; we are looking to find a way to incentivize a move toward a more efficient, a more continuous kind of manufacturing that we think offers a lot of potential for preventing shortages by improving the overall quality of manufacturing.

Ms. CHRISTENSEN. Thank you.

Dr. Crosse, would you like to add anything?

Ms. CROSSE. Well, we too heard from industry these—the same concerns and from FDA the same response. You know, FDA has moved increasingly and, now under FDASIA, explicitly is moving to a risk-based inspection decisionmaking process about which manufacturers they should be inspecting with which frequency.

The drugs that are in shortage, the sterile injectables, are inherently risky in their manufacture, and so you would expect there to be a higher level of inspection of those facilities just because of the risk of the product. We, as part of the ongoing work I mentioned before, we are going to be looking at the pattern of inspections that FDA has had across a number of years of these facilities to see if we are seeing any change, because it was a concern raised to us by manufacturers, but the standards, as posed in regulation and guidance, have not changed.

Ms. CHRISTENSEN. Thank you. I have a number of other questions that I will submit for the record, but I have a short one.

Dr. Crosse, the GAO report doesn't focus on shortages of medically important drugs. Can you tell us how closely the shortage characteristics and trends provided in the report are likely to track with or predict those from medically important drugs? Is that something you can focus on in the future?

Ms. CROSSE. We are very—it tracks very closely. We did use a different data source. We used information from the University of Utah Drug Information Service, because they have had a database for much longer, and so we were able to look at trends across time. FDA didn't develop its database until 2011, and we wanted data that would go back to 2007. But the majority, the vast majority of the data that Utah posts are of medically necessary drugs. There is a very close alignment there. There are some differences in the way the two—that FDA and Utah count the drugs, so the numbers may look different even though you are talking about the same drug shortage.

Ms. CHRISTENSEN. And my time is up, so, thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentlelady.

Now recognize the gentleman from Illinois, Mr. Shimkus, 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman.

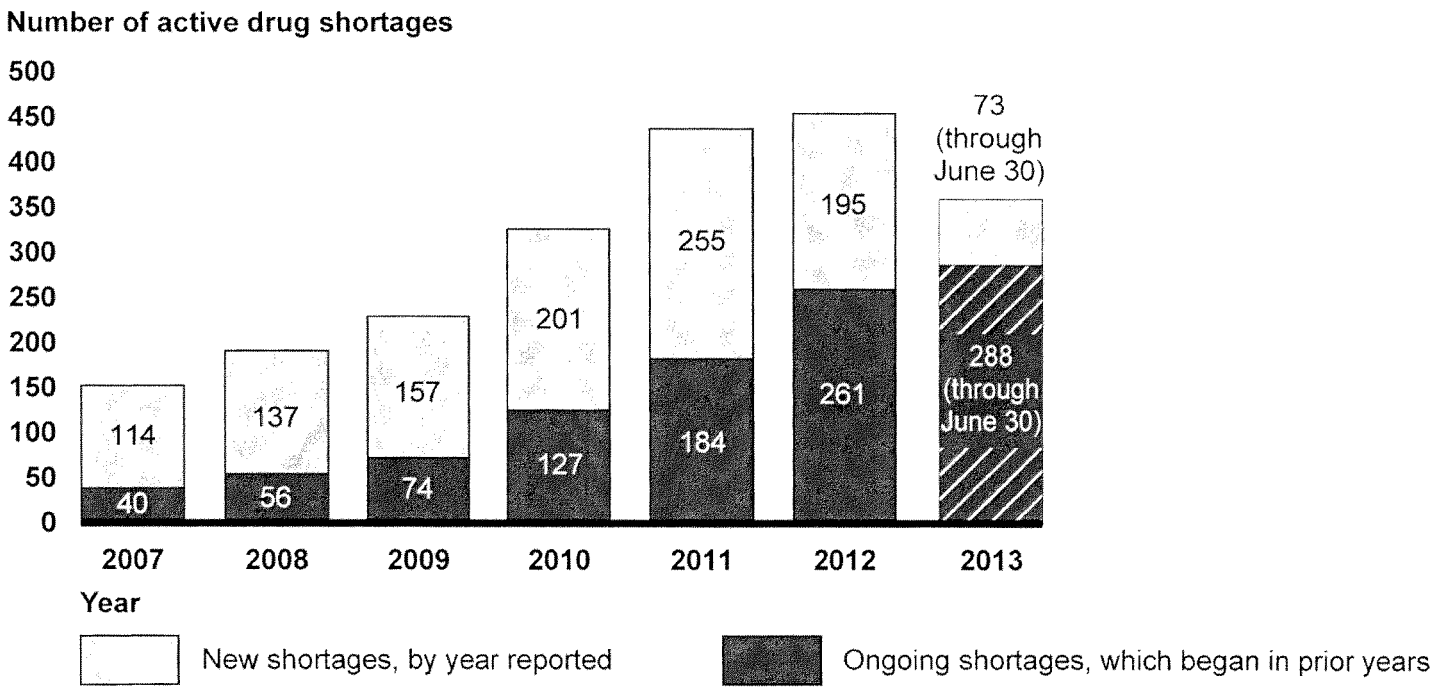
Thank you for being here. And obviously, a follow up to the GAO report. A few comments before I begin. You know, we are never going to have enough money to do whatever we want to do, and more people and more money, sometimes it is just assumed that is going to make things better, but this really—it is important for me to always remember the whole budget pie. When 65 percent is mandatory spending, 35 percent is discretionary spending, if we don't get control of our mandatory spending, spending stays the same, discretionary keeps shrinking, which will affect all agencies, the military and the like.

And so, in this budget debate, as people say, and we hear the discretionary part of the budget, it—we are ill-advised not to always talk about the problems of mandatory spending.

I would also say that FDA was one of the few agencies that got additional money through these budgetary fights than a lot of other agencies.

So, with that, Sydne, can you put up this—because a lot of the questions, I think, are pertaining to this that is in the GAO report. And I have it on—that is why I have been playing around with my iPad, trying to figure out everything that this chart says, but I think it is very illustrative, whether it is Marsha Blackburn or John Dingell, I think they have all been referring to this chart. And the dark blue is ongoing shortages which began in prior years.

[The chart follows:]



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

Mr. SHIMKUS. Now, I guess the first question I have is, so like in the 2000, you have 40. Those don't always carry—some of those must fall off. Is that true?

Ms. CROSSE. Yes, that is—that is true. It is not the same——

Mr. SHIMKUS. Cumulative.

Ms. CROSSE. It is not cumulative of all of them. Some drug shortages are resolved, and so they drop out. Those that have not been resolved by the end of the year roll over into our data for the next year.

Mr. SHIMKUS. And forgive me if I didn't read the report as closely as I should have, from 2007, even until what is projected on the final bar chart, which isn't finished with the fiscal year, are there pending drugs that follow that whole time period?

Ms. CROSSE. There—I am not aware of any that followed the entire time period. We do have some that have extended for 5 years, a very small number. Most drug shortages are resolved within 1 year or 2 years, but there are a very small number of shortages that have continued across multiple years.

Mr. SHIMKUS. Thank you. Now—and so then the lighter blue portion is really kind of, Dr. Throckmorton, that is what you have been referring to, is that success has been made in the new shortages, right? So—and we see that on this chart.

And that is—Dr. Crosse, you have concurred with that, too. There is some—there is progress being made on that, as we can see from that pending chart. Correct? And that is both in the testimony.

Ms. CROSSE. Yes. Yes, that is correct.

Mr. SHIMKUS. So I guess the—so that is my kind of summation. I think this chart is very illustrative in the report and kind of highlighted what most people had talked about.

I guess the—a couple years ago, when we have been having these debates, I always wondered why the market itself doesn't respond to alleviate these shortages based upon a price signal. Now, there—Dr. Burgess kind of mentioned, which Dr. Throckmorton, you may have dismissed that there was a Tamiflu signal sent. I don't know that. You said you didn't know that. Why, in my minute left, is there something structurally about how we, either the government in its coding or its spending through Medicare and Medicaid or the insurance applications of purchasing drugs, is there something that distorts the market signals for shortages?

Ms. CROSSE. I am not sure. You know, we didn't really look at it that way.

Mr. SHIMKUS. That is fair. Maybe that is something, Mr. Chairman, to follow up with in another question in the future.

Dr. Throckmorton, what do you think?

Mr. THROCKMORTON. I think, as others have commented, economics have got to be playing a role in the decisions that the manufacturers are making here. I think we know less about that, at least speaking for myself, speaking for the FDA, than we might like to, but those are important——

Mr. SHIMKUS. A lot of these shortages are low-margin generic drugs, too, so if they are very low margin, they are making a penny on whatever the application is. And that is hard to get a price sig-

nal on a return on a major if you only have one plan operating full speed producing all this product.

Mr. THROCKMORTON. Dr. Burgess' propofol—others would remember better—someone has said that the profit on a dose is in the tens of cents.

Mr. SHIMKUS. Yes, great. Excellent.

Thank you very much. Mr. Chairman, I yield back.

Mr. PITTS. Chair thanks the gentleman.

Now recognize the gentleman from Kentucky, Mr. Guthrie. Five minutes for your question.

Mr. GUTHRIE. Thanks. I appreciate what the gentleman from Illinois is asking because I had a kind of high school reunion with some friends. A friend of mine is an emergency room physician in Auburn, Alabama, and he was telling me about the shortage of drugs. And he said it wasn't the expensive stuff. And he couldn't do his service properly sometimes because of that. And, you know, classic price controls in economics—I am not saying there are price controls, but when there is not ability to move the price for some reason, it is something to investigate—then you would say it is going to be a shortage in quality. That is the two things you mentioned is shortage of ability and quality, and it seems there is not a price signal, that the gentleman from Illinois, to allow other people to enter.

We are not talking about even hundreds of dollars or thousands of dollars. We are talking about sometimes cents and sometimes just dollars, and people aren't getting over that.

But, Dr. Crosse, in your testimony, you noted that FDA officials have told you that FDASIA's requirements that manufacturers notify the FDA in advance have helped the situation that they are able to take some steps, but you also note that while FDA is planning to establish a new information system to track data, there are significant concerns, specifically that they are not conducting routine analysis of existing data, drug shortages in the database to identify or respond proactively. Can you elaborate, or will you elaborate on what——

Ms. CROSSE. Yes. Well, we did have concerns about what we call internal controls, the extent to which FDA was ensuring the accuracy of the information in their database and then the extent to which they were doing broader analyses to look at such things as the ongoing shortages, as opposed to using it as a tool to help them track the status of an individual shortage. So what we weren't seeing were those kinds of larger analyses looking at trends. And as time goes on and they have more fully developed data, we believe it is important for them to engage in that. And they have agreed with us that that is something that they plan to start doing now that they have a little more data for a little longer period of time, that that is something that they can do.

But, you know, we do talk a little bit, to your earlier point, about the, kind of, the economics. That is part of what we are trying to continue to look at. There have been issues raised to us but no agreement on whether or not there is any one source of what is holding down those prices.

Mr. GUTHRIE. OK. Thanks. And so also I noticed, in 2011, inspections were at their peak. FDA inspections were at their peak, and

also the shortages were at their peak. Has GAO examined the correlation between inspections and drug shortages?

Ms. CROSSE. We haven't. And that is also part of what we are going to continue to look at, is to go and see if there was a change across time in inspections. But as I noted before, these are high-risk products for the most part. Most of these are the sterile injectable drugs, and they are high-risk products where you would expect FDA to be going with some greater frequency to those facilities than to someplace that is making, you know, a tablet that has been in operation for a long time with a good safety record.

Mr. GUTHRIE. And then, Dr. Throckmorton, drug shortages often require practitioners to utilize alternative treatments that may not be as effective. Does the FDA compile and disseminate information regarding alternative treatments in times of shortage for practitioners or patients?

Mr. THROCKMORTON. We have typically left that to other groups, particularly the pharmacists and ASHP, for instance, with their Web site that Dr. Crosse has been using for her data and things, do identify alternative uses. We are able to identify other drugs with the same indication, but we recognize the practice of medicine is such that people look for other alternative therapies that may or may not be on label, and so we tend to use the other—where we take advantage of other people's expertise to have them do that for us.

Mr. GUTHRIE. Can GAO 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? And bottom line, are FDA's actions or decisions being exercised consistently?

Ms. CROSSE. I don't know that I can speak to whether they are be exercised consistently. We certainly can provide you with some additional detail on what actions they have taken.

Mr. GUTHRIE. Mr. Chairman, I yield back.

Mr. PITTS. The Chair thanks the gentleman.

I now recognize the gentleman from Virginia, Mr. Griffith, for 5 minutes.

Mr. GRIFFITH. Thank you, Mr. Chairman. I appreciate.

Thank you all for being here today and answering these questions.

I would be remiss to not remind everybody that drug shortages, particularly of sterile injectables, led to some health care providers feeling dependent on the supposedly sterile compounded drugs that ultimately led to the fungal meningitis outbreak in 2012 that killed 64 Americans, including two in my area.

Because these drugs were more difficult to obtain, illegal manufacturers that called themselves compounding pharmacies, like NECC, entered the market to fill the need of hospitals and outpatient clinics for sterile injectables.

Thankfully Congress put the FDA on notice with FDASIA to deal with the drug shortages, much like Congress did with the Drug Quality and Security Act with large-scale compounding and illegal manufacturing.

FDA officials have signalled that the Agency has begun to identify signals to better predict quality issues at manufacturing facilities.

Dr. Throckmorton, can you comment on these improvements?

Mr. THROCKMORTON. Mostly to say that we understand the importance of getting that right, so identifying what those metrics are and then having a discussion about how they would be used is very important. And so part of our ongoing efforts, efforts this coming year and beyond, are to speak with manufacturing experts that can talk about the kinds of measures that a plant uses to follow their own manufacturing quality, understand those things better, and then talk about how a purchaser might make use of those kinds of information.

Mr. GRIFFITH. And I appreciate that, and one of the concerns that I had was that it appeared in that fungal meningitis outbreak that the lawyers at FDA were not using all the powers that were available to them to oversee. And while we don't want too much oversight that stops manufacturers who are doing the right things from producing their product, I am hopeful that the lawyers are being more aggressive if they see something that looks like it is out of line, because while we want to have a good supply, we want to have a safe supply as well. Would you not agree with that, and do you think the lawyers are being a little more aggressive post the outbreak of the fungal meningitis problem?

Mr. THROCKMORTON. I would absolutely agree we need to do anything we can to assure a safe supply.

Mr. GRIFFITH. All right.

Dr. Crosse, GAO recommended that the FDA improve its databases so the Agency can employ more predictive analyses to its preventative activities. How did the Agency respond to this critique, and how far off are they from putting your recommendations into practice?

Ms. CROSSE. FDA agreed with our recommendations, and my understanding is they are beginning to do it immediately.

Mr. GRIFFITH. All right. Also, the GAO report found that the FDA lacked policies, procedures and specific training materials related to management and use of its existing drug shortage database. What impact does this have on the Agency's ability to use this database to prevent or mitigate shortages?

Ms. CROSSE. Well, we think they do need to have these kind of standard procedures in place to assure the accuracy of the data and the understanding on the part of their staff of exactly how data should be entered and how it should be analyzed. They also agreed that they would move forward on those steps.

Mr. GRIFFITH. I appreciate it. What role do you think this database could play in addressing future drug shortages?

Ms. CROSSE. Well, we think it is important for the Agency to have good information because they need to be able to look at this more broadly, to look within classes, to look across time to see, to be able to measure whether or not they are putting the right steps in place and having the kind of impact to improve the situation rather than treating these as each individual kind of situation that has to uniquely be solved.

Mr. GRIFFITH. I appreciate it. Thank you very much.

With that, Mr. Chairman, I yield back.

Mr. PITTS. Chair thanks the gentleman.

I now recognize the gentlelady from North Carolina, Ms. Ellmers. Five minutes for questions.

Mrs. ELLMERS. Thank you, Mr. Chairman, and thank you to our panel for being here today. In my district, this is a very specific situation and I am hearing from all of my hospitals. In particular, I will focus on Wake Med Hospital System. They are an 870-bed health care system with multiple facilities around Raleigh, North Carolina. They basically deal with the three primary vendors for IV infusions. And all three have experienced quality manufacturing issues as well as holiday production shutdowns that contributed to the shortage. Wake Med's pharmacy spent an additional $80,000 in January to stock up on the drugs in anticipation.

I appreciate the efforts of the FDA to address the shortage, but it appears that they are only addressing the symptoms and not the real causes.

I am also concerned about the Medicare reimbursement system, especially the explosion of the 340(b) discounts, which is reducing margins for generic manufacturers. This is pushing them to stop producing low-cost generic injectables, just like the system is driving community cancer clinics into hospitals. It also appears that these manufacturers simply don't have the margins to invest in their manufacturing plans, which is why we see many of the quality problems.

My question has to do with what is and how are we addressing these issues right now. I want to focus my questions today on the FDA's work with the industry to make sure everyone is working together to find solutions.

Dr. Throckmorton, there remains virtually no transparency in the process for how drugs that make it onto the shortage list ultimately get off this list. How does the Agency decide that a product is no longer in shortage, and is there a consistent and standardized formula for FDA uses to produce a product from the shortage list?

Mr. THROCKMORTON. The short answer is, yes, we do have a consistent process that we use to apply to drugs to decide when they come onto the shortage list and when a shortage is no longer existing and they can come off.

Our focus is on determining whether or not patients in the U.S. can get the treatments that they need. So it is not focused on product-by-product shortage, so there may be a shortage of a buffered aspirin because one manufacturer of a kind of buffered aspirin may no longer be manufacturing. But there may be four other kinds of aspirin that are available. That will not be a shortage from our perspective because the other products can and will ramp up. That is something our people know about, talk with those other manufacturers, were able to assess using prescription data, using other data that we have access to; we can determine whether those other manufacturers can fill in for that manufacturer that has made a decision to not manufacture or needed to stop manufacturing to improve a plant or improve a product line.

That is slightly different than the kinds of data that the University of Utah counts, the data that Dr. Crosse is referring to. We are looking at the totality of the data, the availability of a given ther-

apy, not an individual product. And so our numbers are slightly different than ASHP that the University of Utah have.

We believe fundamentally ours reflect the availability of the therapy for the patients, which is our public health goal, if you will. But behind that, we have a process in place to determine when available production is not able to meet demand and then work with manufacturers, and when production returns and is once again able to meet demand, to take something off of the shortage list.

Mrs. ELLMERS. OK.

Also, very specifically, there again, Dr. Throckmorton, the FDA's inspection of API can remain a barrier and ANDA holder can market the generic drug. How has the Agency tried to improve its record on this issue to ensure that the ANDA holders can market a drug and potentially address a drug shortage?

Mr. THROCKMORTON. Two parts to that answer. The first part would be some of the actions that we have already talked about, the expedited reviews and some of the expedited inspections that the FDA is being able to do, particularly in shortage situations.

There is a second longer term, and it relates to the passage of GDUFA. So the Generic Drug User Fee Act has provided us additional resources and additional opportunity to sort of balance the playing field, if you will, so that we are able to devote the resources we need to the generics market, which—85 percent of the U.S. drug market is generics now. We are able to allocate the resources that we need to that area to make certain they are getting the inspectional attention, the compliance history, the reviews from our reviewers that they need to, so that is an important addition for us.

Mrs. ELLMERS. Thank you so much.

And I see my time is expired. Thank you, Mr. Chairman.

Mr. PITTS. Chair thanks of the gentlelady.

That concludes the questions of the members who are present. We will have additional questions we will send to you in writing. If you would please respond promptly.

I remind members that they have 10 business days to submit questions for the record, and members should submit their questions by the close of business on Tuesday, February 25. Thank you very much for the testimony, the good information, and we look forward to continued work with you.

With that, without objection, the subcommittee is adjourned.

[Whereupon, at 3:15 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

Opening Statement of Chairman Fred Upton
Health Subcommittee Hearing on "Examining Drug Shortages and Recent Efforts to Address Them"
February 10, 2014

Thank you for holding today's hearing on drug shortages - the first hearing we have held on this significant, ongoing public health threat since passage of the bipartisan Food and Drug Administration Safety and Innovation Act (FDASIA). This breakthrough agreement last Congress provided FDA with important new authorities and responsibilities to help prevent and mitigate drug shortages. I am eager to hear how they have been utilized and what measures can be taken to ensure doctors have access to every necessary treatment to care for their patients.

As required by FDASIA, FDA submitted its first annual progress report to Congress last week, providing an overview of actions the agency has taken and the progress made to date. We look forward to hearing more about that progress today.

Also, pursuant to FDASIA, this morning the Government Accountability Office (GAO) issued a final report on drug shortages. The report contains a thorough assessment of the many factors that could lead to drug shortages. In the report, GAO also examines the role of FDA and makes several recommendations about how the agency could

improve on its efforts.

Fortunately, the number of new drug shortages was down in 2012 and again in 2013. While this is certainly a positive sign that things may be moving in the right direction, we know a great deal of work remains. Drug shortages have recently plagued our health care system on many levels, from newborns not receiving their necessary nutrients to cancer patients receiving alternative therapies that may be less effective. Now we are hearing of the impact saline shortages are having in hospitals throughout the country. Our work will continue until all patients receive the medications they need and the peace of mind they deserve.

I yield the balance of my time to _____.

Opening Statement of Rep. Henry A. Waxman
Ranking Member, Committee on Energy and Commerce
Hearing on "Examining Drug Shortages and Recent Efforts to Address Them"
Subcommittee on Health
February 10, 2014

Thank you, Chairman Pitts, for holding this important hearing today.

Drug shortages are a continuing problem. The Committee has tackled this issue in a bipartisan manner, and I am confident that we shall continue to do so.

Since our last hearings on this topic two years ago, Congress passed bipartisan legislation addressing drug shortages, the FDA Safety and Innovation Act (FDASIA).

FDASIA requires companies to notify FDA six months before discontinuing the manufacture of a medically important drug. It also requires companies to notify FDA of meaningful disruptions in the manufacture of such a drug.

It requires GAO to issue a report on the causes of drug shortages and to make recommendations on how to prevent and alleviate such shortages.

And it requires FDA to maintain an up-to-date list of drugs that are in shortage, to develop a strategic plan for preventing and mitigating drug shortages, and to publish a regulation defining certain terms used to determine whether a drug is subject to notification.

FDA has the authority to subject biological products, such as vaccines, to the notification requirement if this would benefit public health. I was gratified to see in the draft regulation that FDA intends to make biological products subject to notification.

These were all important steps. However, we knew when we passed the legislation that it would not be a cure-all. And as we will hear today, it has not been.

The good news is that FDA has been able to prevent hundreds of shortages with its new authorities. The number of new shortages that began in 2012 was lower than the number that began in 2011, and the number of new shortages that began in 2013 appears to be lower than those that began in 2012. The bad news is that shortages continue to be a significant public health problem.

For example, a recent survey found that roughly 60% of pediatric hematologists and oncologists have had to alter therapies in response to drug shortages. Neonatologists continue to face shortages of ingredients for life-saving total parenteral nutrition for babies who cannot yet eat and have no other source of nutrition.

Shortages affect a broad spectrum of critically important drugs, including oncology drugs to treat lymphoma, leukemia, and breast and other cancers; anesthesia drugs, without which

surgeries have to be postponed; antibiotics to remedy life-threatening bacterial infections; and vaccines to prevent disease. Without these drugs, patients' lives are at risk.

According to the GAO report, about 60% of drug shortages are of sterile injectable drugs. These drugs are technically difficult to make and each drug is usually manufactured by only one or a handful of companies. If any one company develops manufacturing problems -- which is not uncommon -- other companies may have little excess capacity to help fill the need. These problems can be magnified when sterile injectable drugs are manufactured in aging facilities by generic drug companies whose low profit margins make it difficult for them to invest in upgrading their plants.

But the shortages are not limited to generic drugs. GAO reports that more than a quarter of sterile injectable drug shortages were of brand drugs not available as generics. And about a third of oral drugs in shortage are brand drugs not available as generics. We need to understand what is causing these shortages.

I want to thank FDA and GAO for being here, and look forward to their testimony.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
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Majority (202) 225–2927
Minority (202) 225–3641

March 6, 2014

Dr. Marcia G. Crosse
Director
Health Care
U.S. Government Accountability Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Dr. Crosse:

Thank you for appearing before the Subcommittee on Health on Monday, February 10, 2014, to testify at the hearing entitled "Examining Drug Shortages and Recent Efforts to Address Them."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Thursday, March 20, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

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

Attachments

U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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,

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.

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

[2]See 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

[3]A 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

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[4]A 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).

[5]An 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,

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

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

[9]GAO/AIMD-00-21.3.1.

[10]GAO/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.

[11]On October 31, 2011, the President issued an Executive Order that directed FDA to use its authority to encourage manufacturers to report drug supply disruptions earlier, 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.

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

[13]See 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.

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[14]Federal 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).

[15]According 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.

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

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115

March 6, 2014

Dr. Douglas C. Throckmorton
Deputy Director for Regulatory Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Throckmorton:

Thank you for appearing before the Subcommittee on Health on Monday, February 10, 2014, to testify at the hearing entitled "Examining Drug Shortages and Recent Efforts to Address Them."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Thursday, March 20, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

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

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

JUN 5 2014

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the February 10, 2014, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "Examining Drug Shortages and Recent Efforts to Address Them." This letter is a response for the record to questions posed by certain Members of the Committee, which we received on March 10, 2014.

If you have further questions, please let us know.

Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning, and Legislation

Enclosure

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

We have restated each Member's questions below in bold, followed by our responses.

The Honorable Joseph R. Pitts

1. What is the current ANDA backlog today?

As of October 1, 2012, the Abbreviated New Drug Application (ANDA) Backlog was identified as 4729. The ANDA backlog is defined as the queue of original ANDAs, ANDA amendments, and ANDA supplements pending as of October 1, 2012, that have not received their first action. As of April 1, 2014 the current ANDA backlog requiring a first action is 2,364 and the number remaining to obtain a Refuse to Receive, Withdraw, Approval, or Tentative Approval is 3444.

2. What is the framework that determines the order of how approvals get expedited if on the shortage list? How does expedited approval impact review times?

Shortage-related ANDAs are accorded heightened-review priority relative to other pending submissions. Applications involving non-generic drugs, including new drugs as well as biologics regulated by the Center for Drug Evaluation and Research (CDER), also receive expedited review to address and prevent shortages identified by CDER. Expedited review generally reduces review times. CDER's Office of Generic Drugs (OGD) is in the process of revising its Manual of Policies and Procedures (MAPP) to clarify how ANDA submissions will be prioritized to address public health needs, including drug shortages. MAPPs are internal policies that are disclosed to the public. We plan to conduct webinars, and we would be happy to brief you, when we issue the new MAPP on prioritization of ANDA submissions.

3. The recently enacted Drug Quality and Security Act (DQSA) allows for outsourcing facilities to produce copies of drug products when they are on FDA's Drug Shortage list. How does FDA envision such facilities playing a role in the drug shortage space?

Drugs in shortage can be compounded by an "outsourcing facility," if the facility is compliant with the conditions of section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), which became law on November 27, 2013, as part of the DQSA. Outsourcing facilities are subject to current good manufacturing practice (CGMP) requirements; will be inspected by FDA according to a risk-based schedule; and must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound. If the drug appears on the FDA drug shortage list at the time of compounding, distribution, and dispensing, and the drug product is otherwise compliant with the conditions of section 503B, such drug may be compounded by an outsourcing facility.

4. DQSA also addressed quality and accountability in the supply chain. How does FDA anticipate this law will impact the grey market that has emerged as a result of drug shortages?

Title II of DQSA, the Drug Supply Chain Security Act (DSCSA) outlines critical steps to build an electronic, interoperable system over the next 10 years to identify and trace certain prescription drugs as they are distributed within the United States. While the system established under DSCSA will enhance FDA's ability to help protect U.S. consumers from exposure to drugs that may be counterfeit, stolen, contaminated, or otherwise harmful, it will not solve the root causes of drug shortages. The new system may help members of the supply chain to improve detection and removal of potentially dangerous drugs from the drug supply chain, which may include diverted products from the grey market.

5. What is FDA doing to help generic drug companies that manufacture sterile injectable products come back up to full productivity?

FDA's mission is to ensure that safe and effective drugs are available to the American public by protecting consumers from unsafe, ineffective, and poor-quality drugs. We do this for all drug products, including sterile injectables, by:

- Addressing public health risks associated with legal violations.
- Developing and overseeing drug compliance programs designed to reduce consumer exposure to risks of unsafe and ineffective drugs.
- Monitoring the quality of human drugs through inspectional coverage, product testing, and other pre- and post-market surveillance activities.
- Advising the CDER Director and other Agency officials on regulatory and enforcement issues involving human drugs.
- Coordinating Center-Field relations and providing support and guidance to field offices on case development and regulatory actions.
- Ensuring uniform interpretation of standards.
- Developing policies and compliance strategies to ensure that over-the-counter and prescription drugs are of high quality, properly labeled, safe, pure, and meet applicable drug approval requirements.
- Developing policy and standards to achieve high-product quality through application of CGMP requirements. We accomplish this by coordinating surveillance and pre-approval inspections.
- Coordinating evaluation and classification of drug recalls and working with field offices for implementation of recalls.
- Monitoring resolution of drug shortage situations involving compliance issues.
- Implementing programs and projects to identify, assess, and prioritize the public health significance of legal violations.
- Developing and using innovative enforcement strategies to reduce public health risks associated with legal violations.

As part of the drug shortage mitigation process, FDA offers assistance to firms that are having difficulties that could lead to or put them at risk for shortage. For example, the agency works with firms that request guidance on their plans to address quality or safety issues. And, when firms submit applications to change their manufacturing lines or add capacity that could help address a shortage, FDA expedites review.

When a manufacturer of any sterile injectable, whether generic or not, has a decrease in productivity due to product quality issues, FDA stands ready to work with the manufacturer to the best of FDA's ability.

a. **Is FDA willing to have ongoing dialogues with firms while they are implementing corrective actions to assure that FDA is in agreement with the firm's actions?**

Yes, FDA is willing and does have such ongoing dialogues.

6. **From a quality control perspective, and in the interest of working collaboratively with manufacturers to address this ongoing public health threat, does FDA provide industry with recommendations for addressing potential problems or manufacturing deficiencies to satisfy the FDA's expectations? What other new methods of collaboration is FDA exploring?**

Under the new notification requirements enacted as part of the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA is continuing to receive early notifications of potential manufacturing problems and deficiencies. When FDA becomes aware of these issues, it is part of our process to work closely with the manufacturers to address the problems so that shortages can be prevented whenever possible. FDA works closely with manufacturers on remediation efforts as well, and encourages manufacturers to engage in best practices to avoid or mitigate shortages. Furthermore, as outlined in the Strategic Plan[1] submitted to Congress in October 2013, FDA is working with industry and other stakeholders to identify positive incentives to promote and sustain manufacturing and product quality improvements. FDA is also considering risk-based approaches to identify early warning signals for manufacturing and quality problems to prevent supply disruptions.

FDA, through inspections, seeks to verify industry's conformance to regulatory standards. FDA guidance documents provide detailed recommendations for complying with most of the good

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[1] Title X of FDASIA directs FDA to develop and submit to Congress a Strategic Plan to enhance FDA's response to preventing and mitigating drug shortages. It can be accessed at *http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf*

manufacturing practice regulations. FDA investigators discuss each inspection finding with representatives of an inspected facility, and explain their observations and FDA policies and recommendations at the closing of an inspection. FDA also provides feedback when firms submit post-inspection responses regarding planned or ongoing corrective and preventative actions. When a drug is in shortage, FDA increases the level and frequency of communication with involved facilities.

7. **Many of the current good manufacturing practices (CGMP) regulations date back to the 1970's.**

   a. How have the Agency's standards evolved in the past four decades regarding inspections?

   b. How do you communicate new principles and standards to industry and FDA inspectors?

   c. Does the Agency have plans to increase transparency with respect to FDA's expectations on this front?

FDA has revised the CGMP regulations at 21 CFR Parts 210 and 211 many times since the last major revision in 1979. FDA has issued dozens of new and revised CGMP guidance documents in the last two decades to provide current, detailed information to staff and industry about compliance with regulatory requirements and quality standards. FDA's inspection standards also evolve over time, with the last major revision taking place in 2002. Since 2002, FDA's drug inspection program provides for "systems-based" coverage that allows FDA investigators to perform abbreviated inspection coverage in lieu of a full inspection at facilities with a compliant history. Moreover, since first developing a risk model in 2004, FDA has utilized a risk-based approach to prioritize facilities for routine inspection. Currently, FDA is actively reviewing several of its drug quality inspection programs, including the primary inspection program for most human drugs. The inspection program for sterile drugs produced by aseptic processing was last revised in 2012.

All FDA regulatory standards and recommendations are published in accordance with the requirements for establishing regulations and issuing guidance that apply to all Federal agencies. FDA also conducts outreach to the public and affected industry by presenting at industry technical meetings, working collaboratively with other regulators and industry to provide training opportunities, and responding to stakeholder inquiries. All FDA regulations and guidance documents, both draft/proposed and final, are posted at *www.fda.gov*.

8. **Are there ways to enhance communications to practitioners regarding the expected duration and severity of a drug shortage, taking into account information based on manufacturing production, historical product demand in the market, and the severity of the issue impacting production and expected time line for resolution? For example, utilizing group purchasing organizations' (GPOs) and wholesalers' information**

regarding market demand based on historical usage of a product, which would allow practitioners to better allocate product and the ability to seek therapeutic alternatives when available.

FDA continues to enhance our communications to practitioners and other stakeholders affected by drug shortages. The most straightforward and accessible method for improving communication with these groups has been through FDA's website. FDA posts information on the website regarding the expected duration and severity of each shortage, including information received from manufacturers. FDA encourages firms to provide us with as much detail as possible for posting on the FDA website. FDA utilizes data purchased from IMS Health to help determine market demand and also communicates regularly with GPOs, wholesalers, and other stakeholders as needed. In response to feedback from numerous stakeholders, FDA has significantly improved its drug and biologics shortage websites in the past year and will continue to make enhancements based on continued communications with outside groups. For example, in response to stakeholders' feedback, the FDA drug shortage website is now able to be sorted by therapeutic categories to make it easier for healthcare professionals to find information about the drugs impacting their specialty.

9. **Would the FDA be willing to communicate more frequently on the topic of worldwide production capacity of drugs in short supply with the purpose of expediting approval into the United States?**

FDA continues to monitor the production capacity for drugs in shortage made for the U.S. market. Within its authorities, FDA is actively working with manufacturers to increase supplies of drugs that could help prevent or address a shortage. In cases where there is limited production capacity and additional capacity is needed to address or prevent a shortage, FDA expedites review of applications from manufacturers that could help address a shortage by adding production lines, additional suppliers, or manufacturing sites. FDA also expedites review of new applications for drugs that are in shortage or at risk of shortage. Out of the 118 ANDAs OGD expedited during the period of 1/1/2013 – 9/30/2013, 62 were original applications and 56 were supplemental applications to address a drug shortage.

10. **Please provide an update regarding the saline shortage.**

Following is an update on the saline shortage as of April 28, 2014 (from FDA's web site at *http://www.fda.gov/Drugs/DrugSafety/ucm382255.htm*):

In response to the ongoing shortage of 0.9 percent sodium chloride injection (normal saline), Baxter Healthcare Corp. of Deerfield, Ill., will temporarily distribute normal saline in the United States from its Spain manufacturing facility. FDA is temporarily exercising its discretion regarding the distribution of Baxter's saline product from Spain and Fresenius Kabi's saline product from Norway as needed to address this critical shortage, which poses a serious threat to patients.

FDA inspected Baxter's Spain facility where its normal saline product is made to ensure the facility meets FDA standards. FDA asks that health care professionals contact the Baxter directly to obtain the product.

In addition to these sources of normal saline, U.S.-based manufacturers—Baxter Healthcare Corp., B. Braun Medical Inc., and Hospira Inc.—are currently producing and releasing normal saline. Baxter's saline product from Spain will be distributed temporarily in addition to Baxter's FDA-approved version that is currently manufactured and distributed in the United States.

While the shipments described above will help reduce current disruptions, they will not resolve the current shortage of 0.9 percent sodium chloride injection. Preventing drug shortages is a top priority for the FDA, and we are doing everything within our authority to improve access and alleviate this shortage.

The Honorable Henry A. Waxman

1. **In looking through the FDA testimony and the FDA report to Congress on drug shortages for calendar year 2013, I noticed that the number of shortages reported by FDA were different from those in the GAO report. Please explain the basis for the differences, and the implications of those differences. I am particularly interested in the relative utility of the two difference sets of data for assessing the relative public health impacts of existing shortages (both new and ongoing) and the relative success of FDA and industry efforts to address those public health impacts.**

FDA works very closely with the University of Utah (Utah), whose data GAO cites, and coordinates on information sharing. Nonetheless, our numbers are different because our databases were set up for different reasons and, therefore, track shortages differently.

The Utah database was set up by the American Society of Health-System Pharmacists (ASHP) to help pharmacists identify which specific product codes/product versions are stocked out. For this reason ASHP will report a shortage of a particular drug, if any version (NDC) of a product by any manufacturer is not available. ASHP will generally consider the shortage active until every version by every previously participating manufacturer is back in supply. This inventory management perspective makes sense from ASHP's standpoint because this information is relevant to their main constituents, who are pharmacists. ASHP has used this method consistently since they began tracking pharmacy stock-outs.

In contrast, the purpose of FDA shortage tracking is to identify products in shortage from a public health perspective. We consider a drug to be in shortage when the supply from all providers is not sufficient to meet the demand or projected demand. This public health perspective has implications for both how FDA determines whether there is a shortage, and how we determine that a shortage is resolved. For example, suppose that a particular manufacturer cannot produce the 5 milligram (mg) dose of a drug, but another FDA-approved manufacturer can make up that difference on an ongoing basis. Even though the first product version is out of stock, FDA will consider this a resolved shortage because there is no longer a gap between the

supply and demand of therapeutically equivalent product. In contrast, ASHP would still consider this shortage active because the first manufacturer's product was not back on the market.

The varying objectives of the two databases and the way they receive reports from stakeholders have implications beyond how the active status of a shortage is defined. For example, ASHP will capture reports by pharmacies of regional stock-outs. ASHP will also report stock-outs of products whose lack of availability would not necessarily adversely affect patient treatment. For example, a stock-out of Clarinex D, an allergy medication with many good therapeutic substitutes, would be listed on the ASHP website, but the stock-out might not be reported to FDA and, therefore, would not be tracked by FDA.

2. **Neither the FDA testimony nor the FDA report to Congress contained data on ongoing shortages. Please explain why FDA did not provide such data, and provide whatever such data you have been able to compile. If you are able to provide such data, please explain why.**

An important focus of FDA has been to address potential drug shortages, so that they do not turn into actual shortages. Our successes in this work have been summarized in both FDA's testimony and FDA's Report to Congress.[2] Recognizing the importance of shortages that do occur, FDA has also compiled data for ongoing shortages going back to the end of 2010. This analysis will aid us in our work to address drug shortages going forward. At the end of 2010, there were a total of 47 ongoing shortages. This number increased to 99 ongoing shortages at the end of 2011 and further increased to 121 ongoing shortages at the end of 2012. As of December 31, 2013, the number declined to 97 ongoing shortages. Thus, in contrast to the University of Utah data, which leave many shortages as active because even one NDC has not been restored, FDA's public health-oriented metric shows that ongoing shortages have begun to decline.

3. **Please describe the criteria by which FDA considers a shortage to be ongoing, and by which FDA considers such a shortage to have ended. Please compare and contrast these criteria with those used or relied on by the General Accounting Office (GAO) for calculating ongoing shortages, and the implications of the different approaches for determining progress in mitigating shortages of public health significance.**

The ongoing shortages compiled at the end of each calendar year include the shortages which began in that year as well as those that began in previous years and persisted. FDA's data for ongoing or active shortages differs from the numbers compiled by the University of Utah Drug Information Service (Utah). The Utah numbers are used by ASHP for their website postings and

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[2] The Report to Congress summarizes the major actions FDA has taken to prevent or mitigate drug shortages in the United States from Jan. 1, to Sept. 30, 2013, and information about shortages that occurred. This report is required under FDASIA, and is available at *http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm384891.htm.*

were used by GAO in their February 2014 Drug Shortages report.[3] Utah reports a higher number of ongoing shortages than FDA does. As discussed above, this is because Utah considers a drug to be in ongoing shortage when one or more manufacturers are no longer making all NDCs previously associated with the drug, even if the remaining manufacturers have increased production to meet the entire shortfall. FDA tracks the total supply from all manufacturers and considers a shortage to be resolved when the total supply is adequate to meet demand and projected demand.

4. **Is FDA able to distinguish between shortages that have significantly mitigated and those for which there has been little or no mitigation? Is such distinction useful in evaluating the relative success of FDA and industry in addressing drug shortages?**

FDA is able to track the level of mitigation for a particular shortage by monitoring the supply status of the manufacturers involved and how much production output is occurring relative to historical market demand. We believe any shortage of a needed drug is important, and FDA continues to take all possible actions to mitigate shortages until all demand is being met and at that time the shortage can be moved to the resolved section of the FDA website.

The implication of this metric is that a shortage is considered active even if supply is restored to the point that it almost, but not quite, reaches historical demand. In that sense, the current metric tends to overstate the severity of drug shortage problem. FDA is exploring potential metrics that might measure shortages more precisely.

5. **Please provide a fuller explanation of HHS' concern, as indicated in its comment to GAO reproduced in Annex V or the GAO report, that GAO's presentation of data on ongoing shortages may overstate the drug shortage problem. The comment to which I am referring states that HHS is "concerned that the data presented by GAO may overstate this problem by counting any shortage where not all National Drug Codes have been restored by all manufacturers as an ongoing shortage. This overstates shortage persistence because there are many instances where not all manufacturers are producing all product codes but the manufacturers that are currently producing the drug have increased production of their product codes to meet all demand."**

As described in the responses to Questions 1 and 3, Utah data would count a drug as being in shortage if a particular product from one manufacturer is out of stock, even if the total supply of the drug from all sources is able to meet demand. The Utah data appropriately captures the stock-outs that may affect pharmacy inventories, but such an approach overstates the public-health impact of shortages. For example, if tablets of Drug X from Firm A were no longer be available, this would be reflected as a shortage in both the FDA and Utah data. However, if Firm B starts to produce the Drug X under an ANDA, so that providers can readily obtain Drug X,

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[3] Available at *http://www.gao.gov/assets/670/660771.pdf*

FDA would consider the shortage to be resolved, while Utah would continue to list it as a shortage.

6. **One of the reasons sometimes given for the large increase in drug shortages in 2011 is that FDA has become "much more aggressive in their inspection formats over the past two to four years."[4] A 2012 staff report of the Committee on Oversight and Reform contains an FDA graph of 2011 enforcement statistics, showing a significant increase in numbers of FDA warning letters in 2010 and 2011, correlating at least generally with the increase in drug shortages in that same time period.[5] At our hearing, some Members also noted the correlation between increases in warning letters and increases in drug shortages. Please provide data and information relevant to evaluating the validity of the notion that the dramatic increase in drug shortages seen in 2010 and especially in 2011 may be due in some significant part to the increase in FDA warning letters in that same time period, as shown in the FDA graph reproduced in the Oversight staff report. Please include the numbers of CDER warning letters, and in particular, the numbers of CDER drug manufacturing warning letters (which presumably would have the most relevance to drug shortages), in the years leading up to, and extending after, the peak of drug shortages in 2011, and compare them with the numbers of drug shortages in those same years.**

The increase in FDA Warning Letters cited by the Committee's report between 2010 and 2011 was unrelated to drug shortages; it was due primarily to the actions of the relatively new Center for Tobacco Products (CTP)(see Graph 1 below. The Agency was given authority over tobacco products by Congress in June 2009, and in 2010 and 2011, began contracting with states to inspect retailers for compliance with the FD&C Act. CTP issued 1,040 Warning Letters in 2011; 60 percent of all Warning Letters issued that year.

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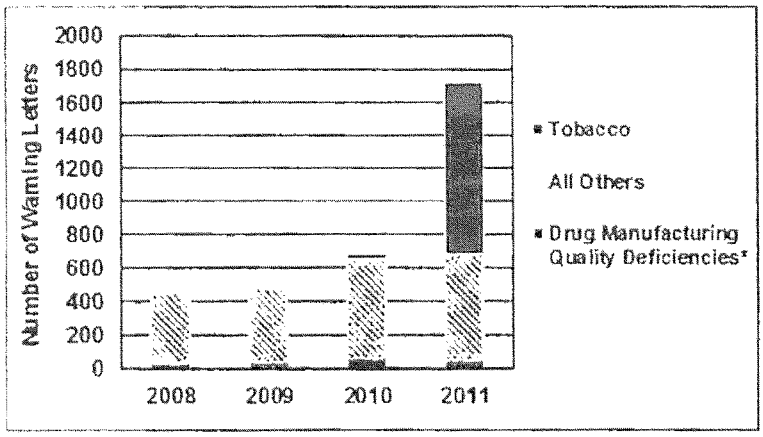
[4] Attributed to David Gaugh, Senior Vice President for Regulatory Sciences at the Generic Pharmaceutical Association, in House Committee on Oversight and Government Reform, *FDA's Contribution to the Drug Shortage Crisis* (June 15, 2012) (online at *http://oversight.house.gov/wp-contentuploads/20 J 2/06/6-15-20 12-Report-FDAsContribution- to-the-Drug-Shortage-Crisis.pdf*).

[5] House Committee on Oversight and Government Reform, *FDA's Contribution to the Drug Shortage Crisis* (June 15, 2012) (online at *http://oversight.house.gov/wp-content/uploads/2012/06/6-15-2012-Report-FDAs-Contribution-to-the-Drug-Shortage-Crisis.pdf*).

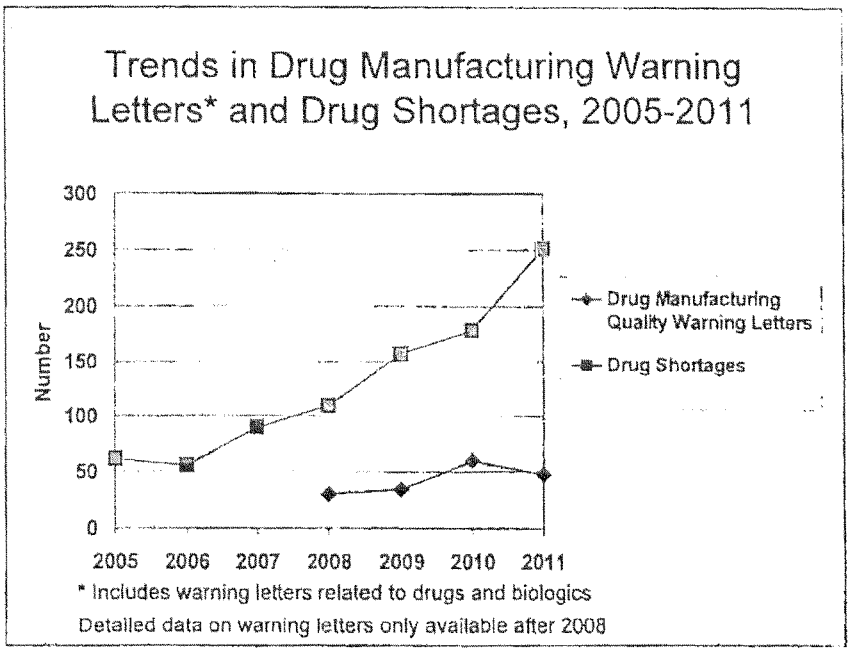
Graph 1



* Includes warning letters related to drugs and biologics

As Graph 2 below demonstrates, from 2008 to 2011—the time period where there was a dramatic increase in drug shortages—the level of Warning Letters issued to firms for quality deficiencies in the manufacture of human drugs or biological products remained relatively flat.

Graph 2



To summarize, the data clearly indicate that the number of Warning Letters relevant to drug products has not increased radically, as the report suggests, and that the increase in total Warning Letters is almost entirely due to Warning Letters issued by the Center for Tobacco Products. These Warning Letters are not the root cause of the increase in drug shortages.

The Honorable Marsha Blackburn

1. **You have said that once you transition to your new information system, you will be better equipped to analyze information and predict and (most importantly) prevent shortages. What are your metrics on this? What will be the percentage decrease in the backlog of drug shortages in six months, one year, and two years?**

The new Drug Shortage Data System (DSDS) aims to enhance the efficiency and consistency of drug shortage data entry. It revises business rules, standardizes key data elements, and adds automated data integrity checks to ensure that data are accurate and complete for analysis purposes. DSDS also centralizes various databases currently used by FDA's Drug Shortages Staff to assess the potential impact of shortages, which products are currently marketed, and what is their market share. This simplifies the data entry process (because it auto-populates certain fields) and streamlines the basic research conducted when a shortage or a potential shortage is reported. FDA is working on backfilling the system with shortages from the last few years and has plans to develop more sophisticated reporting capabilities for analyzing these data.

But because DSDS is simply an enhanced data tracking system, it is not capable of predicting shortages. DSDS only tracks drugs for which FDA received notification that they are in imminent threat of shortage and those that actually went into shortage; it does not track market characteristics of other drugs, which is something that would be needed for a forecasting tool. Also, identifying products at risk of shortage requires information beyond the scope of what FDA is able to access, such as profit margins, production plans, and other business decisions made by firms. Nor can the system suggest what actions DSS should take to resolve shortages—that is appropriately left to the experience and judgment of FDA's Drug Shortages Staff in coordination with other parts of FDA and the existing and potential manufacturers.

Nonetheless, DSDS may have an indirect impact on FDA's ability to mitigate and prevent shortages. For one thing, DSDS streamlines the data entry and basic research process, thereby freeing the Drug Shortages Staff to work on other tasks. The DSDS will also enable FDA to better understand the factors that have been causing drug shortages in the past. Here, the DSDS is one of several sources of data that FDA plans to draw on to better understand shortages. DSDS will make it easier for FDA to analyze what factors differentiate actual shortages from prevented shortages and long-lasting shortages from those resolved relatively quickly (e.g. the reason for shortage, type of technology involved, originating firm, and depth of originating disruption).

Because shortages generally arise from and are ultimately resolved by manufacturing changes, we cannot say with much precision by how much drug shortages are going to fall in six months or a year. We can say that the number of new shortages was lower in 2013 than in 2011 and that the number of ongoing shortages was lower at the end of 2013 than at the end of 2012. Absent significant demand or unexpected changes in supply (supply shocks), we do anticipate that shortages will continue to fall as companies upgrade their facilities and restore production as planned.

2. **When do you plan to implement the recommendations made by GAO to develop policies and procedures for the use of the existing drug shortages database (and, ultimately, the new drug shortages information system) to ensure that staff enters information into the database in a consistent manner and to ensure the accuracy of the information in the database? Can we expect that to happen within the next six months, one year, and two years?**

FDA is in the process of documenting all the data fields and the general data entry process. We are also updating the training materials already created for the launch of DSDS. We anticipate having documentation for the current modules completed within six months.

The Honorable John D. Dingell

1. **What is FDA's perspective on the adequacy of current methods of public communication regarding available remedies for drug shortages? Are patients and practitioners who are affected by drug shortages fully aware of available remedies?**

FDA continues to enhance our public communications through improvements to the FDA website. For example, FDA's web site now includes the following features:

- More frequent updates to the CDER shortage website, including biweekly updates on information from manufacturers about progress on specific shortages
- Icons to highlight *new* listings and *update* dates
- Improved layout for easier navigation, including the creation of a Current Drug Shortage Index, and separating the shortage list into sections of the alphabet for each page
- Information about the causes of shortages
- A page for additional news and information, such as extensions of expiry date for a specific lot of product to address a shortage
- A subscription form allowing individuals to sign up to receive an email each time the list is updated

FDA's website is linked to the website maintained by ASHP and Utah. FDA, ASHP, and Utah exchange information on a routine basis sharing notifications and public information on the status of the drug supply. This collaborative effort has greatly improved FDA's ability to monitor product disruptions. ASHP's website also provides recommendations about therapeutic alternatives.

2. **Even though some of the imported products have not been approved for the use indicated, we know it is being imported at the direction of the FDA, with lot review and clearance. Has the FDA issued any guidance to manufacturers on their ability to educate practitioners on the availability of drugs that have been imported to fill critical shortages?**

When drugs are temporarily imported to address shortages, the importing company generates a Dear Healthcare Professional letter, which contains information about the imported drug, as well as any differences in the imported drug from the FDA-approved version. FDA reviews and posts the letter on the FDA website along with instructions for how to order the drug. The letter also accompanies the drug when it is shipped to hospitals and other facilities. ASHP and other affected stakeholder groups are notified about the temporary import so that they may inform their constituents of the availability as well.

The Honorable Lois Capps

1. **I appreciate the work the FDA has done to curb drug deficiencies across the country. I know you are pleased to see the numbers of those affected by shortages drop, and so am I. However, I am particularly concerned with the effect of shortages on the pediatric cancer population, often because many of the drugs given to childhood cancer patients are older or off-patent. I have heard from clinicians that many of these drugs that have fallen into shortage in recent years do not have interchangeable equivalents. Will you address any particular action being taken to address the shortage of drugs available to treat pediatric oncology patients and if there are any additional authorities that Congress may need to provide to the FDA to more proactively address the shortages in this community?**

Early notification about all possible shortages, as requested in the President's Executive Order 13588 and codified into law by Congress in FDASIA, has enabled FDA to work with manufacturers to restore production of many lifesaving therapies, including drugs needed to treat pediatric cancer. Once notified of a potential disruption in production, FDA can take a number of steps to help prevent or mitigate a shortage, including:

- Determine if other manufacturers are willing and able to increase production
- Expedite inspections and reviews of submissions
- Exercise temporary enforcement discretion for new sources of medically necessary drugs
- Work with the manufacturer to ensure adequate investigation into the root cause of the shortage
- Review possible risk mitigation measures for remaining inventory

FDA also communicates with affected stakeholder groups, including Children's Oncology Group, American Society of Clinical Oncology, and other groups impacted by shortages, so that they can continue to be informed of the situation and the progress being made to mitigate the shortage.

The Honorable Renee Ellmers

1. **When is your parent, HHS, going to tackle the underlying cause of this crisis?**

We would welcome an opportunity to discuss your specific concerns about work that HHS might undertake in addition to the FDA work described above. As outlined in the Strategic Plan for Preventing and Mitigating Drug Shortages, which was submitted to Congress in October 2013, FDA is continuing to work with industry and other stakeholders to address the underlying causes of shortages, including sustaining manufacturing quality. While keeping in mind the role other stakeholders play in ensuring manufacturing quality, FDA is also exploring actions it can take, both alone and in collaboration with other groups. Included in these efforts are the plans to develop methods to incentivize and prioritize manufacturing quality and to identify early warning signals of shortages. FDA is also working with a variety of stakeholders to increase knowledge to develop new strategies to address shortages.

2. **The drug shortage list should not be viewed as simply an administrative task. It must be a predictable and consistent process designed to encourage the entry and retention of FDA regulated manufacturers into these markets. How does the Agency consider this important factor in its decision-making process?**

FDA considers the drug shortage list posted on the FDA website to be a critical communication tool for industry, health care professionals, patients, and other stakeholders. FDA has a process in place for posting shortages on the list, obtaining regular updates from manufacturers, and for moving shortages to the resolved section of the list when the shortage has ended. When a shortage is posted on the list, FDA will expedite review of applications and take other actions which can help resolve the shortage. When a drug is in shortage, FDA works with all manufacturers of the drug on ways to increase production and address the shortage. FDA also works with firms to resolve any manufacturing issues contributing to the shortage. FDA encourages firms to continue making medically necessary drugs in supplies sufficient to meet all U.S. patient needs.

3. **Section 1001 of the FDA Safety and Innovation Act requires 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 requirement in FDASIA. Is that correct? Has the Agency been forced to use their failure to notify letter authority in the statute?**

Early notification has been very helpful in allowing FDA more time to work with manufacturers and other groups to maintain treatment options and prevent drug shortages. After the Executive Order the number of notifications increased to six fold and after the implementation of FDASIA, the number of notifications doubled and currently the number of notification is back to six fold. To date, FDA has not issued a failure-to-notify letter.

4. **Under what circumstances would FDA address a shortage by facilitating the importation of a drug from a foreign manufacturer? Is this option truly a last resort?**

When there is a shortage of a medically necessary drug, FDA's practice has been to first work with the current manufacturers of the drug for the U.S. market, which may include both domestic and foreign manufacturers, to address the shortage. In rare circumstances, when the current manufacturers that make the drug for the U.S. market have not been willing and able to meet patient needs and an ongoing shortage is anticipated, FDA has explored whether there are other manufacturers, domestic or foreign, already supplying the drug to other countries, that may be able to meet patient needs in the United States. FDA has worked with these manufacturers to determine if they have supplies available for the U.S. and are able to provide information to FDA to ensure that the drug is of adequate quality, is manufactured in a facility that meets FDA quality standards, and does not pose undue risks for U.S. patients. FDA has then used regulatory discretion to facilitate importation (if necessary) and distribution of the product, on a temporary basis, to meet critical patient needs during the shortage. The Agency has considered this option only in very limited circumstances. FDA has been reviewing certain aspects of our past practices with respect to importation, in light of the recent decision by the U.S. Court of Appeals for the District of Columbia in *Cook v. FDA* (733 F.3d 1 (DC Cir. 2013)).

5. **Is the Agency's decision to import a particular drug affected if an ANDA for that same drug had already been submitted by a U.S. manufacturer?**

When a medically necessary drug product is in shortage and an ANDA for that drug has been submitted, FDA has made every effort to expedite review of the ANDA and to work with the manufacturer to ensure adequate availability of the product, if approved, to meet patient needs in the U.S. If that process is successful, the shortage may be averted and importation would be unnecessary. FDA has explored alternative sources of drugs in shortage under circumstances described in the response to Question 4.

<u>The Honorable Kathy Castor</u>

1. **Thank you Mr. Chairman for holding this important hearing to examine efforts aimed at reducing the frequency of drug shortages. Drug shortages impact the lives of millions of Americans every year. One particularly serious issue relates to a lack of necessary medicine in hospitals throughout America-particularly at children's hospitals. Within my own district, this problem has grown to critical importance. I have brought up in previous hearings the critical shortage children's hospitals across the country are facing, including All Children's in my district. Among the shortages are sterile injectables which are used to provide vital nutrition to neonates and other pediatric patients. All Children's in particular has experience severe shortages in zinc, calcium chloride, sodium acetate and several others.**

   Dr. Throckmorton, in your testimony you discuss ongoing efforts that the FDA is taking to ensure adequate drug supplies in both the present and future. Given the current

situation, in what ways can the FDA help prevent drug shortages and improve current efforts at children's hospitals throughout the nation?

FDA considers the shortages of sterile injectables used to provide vital nutrition to neonates and other pediatric patients to be of significant public health concern and has used all tools available to address this shortage. The most recent shortage of these products began at the end of 2012, when one large manufacturer of these drugs, American Regent (Luitpold), halted production to address quality problems, including particulate matter in sterile injectables manufactured at the plant. FDA has continued to work with Luitpold to release drugs that were at risk of containing particulate matter, accompanied by a letter included in the package that advised health care professionals to use a filter with the drug to prevent patient harm. FDA has also worked to help make temporary supplies available from additional sources for IV nutrition drugs in shortage, including calcium chloride and zinc injection. We expect that these supplies will continue to be available until the U.S. manufacturers can meet all patient needs. For other drugs that are no longer being made by Luitpold, including sodium acetate, FDA has encouraged other manufacturers to ramp up production to cover the shortfall. In order to prevent these types of shortages from occurring in the first place, FDA has identified important actions, including working to support new manufacturing methods that promise high-quality drug manufacturing that could help to ensure that patients have needed access to lifesaving medicines and revitalize pharmaceutical manufacturing in the United States.

In addition to continuing to address and prevent shortages, FDA has regular communication channels established with the American Academy of Pediatrics as well as the American Society of Parenteral and Enteral Nutrition, and has shared shortage information with these two groups as well as many additional groups impacted by shortages.

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