



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 Plan¹ 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

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

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,

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.**

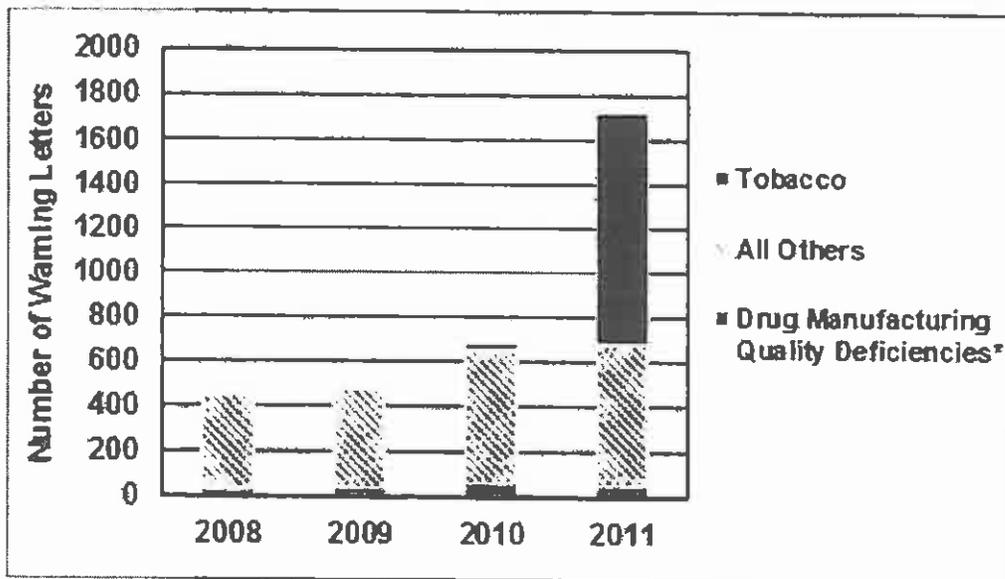
The increase in FDA Warning Letters cited by the Committee's report between 2010 and 2011 was unrelated to drug shortages; it was due primarily to the actions of the relatively new Center for Tobacco Products (CTP)(see Graph 1 below. The Agency was given authority over tobacco products by Congress in 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.

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-content/uploads/2012/06/6-15-2012-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

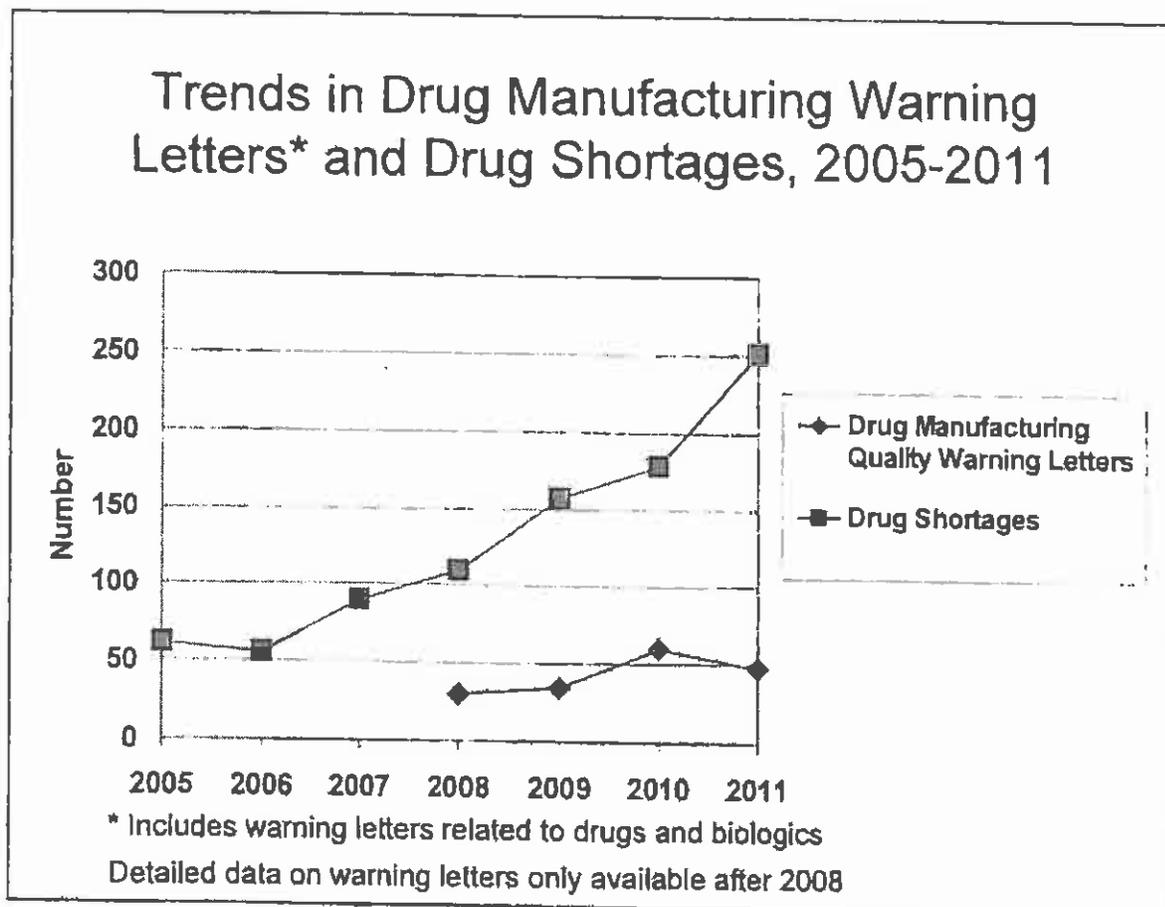
FDA Warning Letters, 2008-2011



* 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.

The Honorable Kathy Castor

- 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.