DEPARTMENT OF HEALTH AND HUMAN SERVICES

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UNITED STATES SENATE

"Prescription Drug Shortages: Examining a Public Health Concern and Potential Solutions"

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INTRODUCTION

Mr. Chairman and Members of the Committee, I am Dr. Sandra Kweder, Deputy Director, Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to be here today to discuss the growing problem of drug shortages. This is a very troubling situation and one that FDA takes very seriously. We are committed to addressing this problem and are eager to continue to work with others to help find short and long-term solutions to the challenge of drug shortages.

Today I will provide background on drug shortages, explain some of the reasons for drug shortages, and discuss FDA's ongoing actions to prevent or mitigate shortages as well as the more recent efforts by the Administration to further reduce and prevent drug shortages. The latter includes an Executive Order issued by President Obama on October 31, 2011, that will help address the shortage of prescription drugs and help ensure patients have access to the life-saving medicines they need.

Background

FDA defines a drug shortage[1] 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 at the patient level. The impact of drug shortages on patients can be significant and even

[1]CDER Manual of Policies and Procedures (MAPP) 6003: *http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM079936.pdf.*

life-threatening. Certain drugs that recently have been in shortage, such as "crash cart" drugs, can literally be lifesaving in the acute setting, while others, such as outpatient chemotherapy drugs, must be administered within days or weeks to provide maximum benefit. Shortages of these drugs not only have an impact on clinical decision-making, but they could also significantly affect patient outcomes. For example, a shortage of propofol, which is used as a sedative and for general anesthesia, led clinicians to substitute etomidate, resulting in eight suspected cases of phlebitis (inflammation in a vein) in a single hospital system. Other drugs that have experienced shortages, such as the cancer drug cytarabine, are important drugs not only because they treat a critical disease, but also because they lack an effective alternative.

In addition, drug shortages are impacting research studies. The National Cancer Institute (NCI) recently reported that while there have been periodic shortages of different cancer drugs over the past several years, nothing has approached the scale of the current shortages of chemotherapy drugs. NCI notes that the inability to obtain adequate supplies of these cancer drugs for research has resulted in promising clinical trials being suspended indefinitely; patient enrollment being abruptly halted; and trials being delayed while alternative treatment regimens are developed.

FDA's awareness of these consequences for patients drives our efforts to prevent and resolve shortages as soon as possible.

The number of drug shortages has been rising steadily over the last five years. In 2005, CDER reported a total of 61 shortages; by 2010, that number had risen to 178.[2] The rising trend of drug shortages has continued into 2011, with 220 shortages tracked by FDA from January through

[2] "A Review of FDA's Approach to Medical Product Shortages Drug Shortage Report": *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm275051.htm*.

October of this year. Although shortages can occur with any drug, shortages of sterile injectables currently make up a large and increasing share of these shortages, despite the fact that sterile injectable drugs comprise a small percentage of the overall prescription drug market. These include critical products such as oncology drugs, anesthetics, parenteral (intravenous) nutrition drugs, and many drugs used in emergency rooms.

Of the 127 drug shortages tracked by FDA during the period from January 1, 2010, to August 26, 2011, oncology drugs accounted for 28 percent of shortages, followed by antibiotics at 13 percent. One hundred eighteen shortages (93 percent) involved medically necessary drugs and 52 of the shortages (41 percent) were both medically necessary and sole-source drugs.[3] For the purpose of prioritizing our work to address shortages, we consider a drug medically necessary if it is used to prevent or treat a serious or life-threatening disease or medical condition for which no acceptable alternative drug is available.

Reasons for Drug Shortages

There is no single reason that drug shortages occur. The Agency has identified a variety of root causes of drug shortages, some of which I will discuss here. Ultimately, in any given drug shortage, many factors are involved, and underlying causes may operate alone or in combination to result in an individual shortage. These include, but are not limited to, industry consolidation, shortages of underlying raw materials, inventory and distribution practices, difficulty in producing a given drug (e.g., sterile injectables, which entail a much more complex

[3] "A Review of FDA's Approach to Medical Product Shortages Drug Shortage Report": *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm275051.htm.*

manufacturing process than solid dosage forms), quality and manufacturing problems, production delays, discontinuations for business reasons, and unanticipated increases in demand.

Of the 127 drug shortages tracked by FDA during the period from January 1, 2010, to August 26, 2011, 50 percent were generic or unapproved drugs[4] (often drugs that have been on the market for decades, but which have never received FDA approval), 43 percent were innovator drugs, and 7 percent had both categories in shortage. Sterile injectable medications accounted for 102 drugs in shortage (80 percent of the total 127) and approximately 54 percent of these shortages were due to product quality issues such as particulates, microbial contamination, impurities and stability changes resulting in crystallization.[5]

Industry consolidation has also contributed to the drug shortage problem. In 2010, the top five generic sterile injectable manufacturers accounted for 80 percent of the sterile injectables sold in the U.S. market by volume.[6] When a firm has a manufacturing or quality problem, they may voluntarily suspend production so they can identify and address the root cause of the product-quality problem. Some of these quality issues are complex and firms need to take significant time to correct the underlying cause of the problem. Such is the case with shortages of older sterile injectables, which involve special techniques and processes to maintain sterility. When one firm experiences a quality problem that results in production holds or slowdowns, the remaining firms are often not able to make up the shortfall, because they have limited manufacturing capacity.

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[4] Unapproved drugs are drugs that have not received FDA approval to be legally marketed.
[5] "A Review of FDA's Approach to Medical Product Shortages Drug Shortage Report": *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm275051.htm.*
[6] "A Review of FDA's Approach to Medical Product Shortages Drug Shortage Report": *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm275051.htm.*

Inventory and distribution practices by manufacturers and distributors can alter the availability of drugs, often creating short-term shortages. Better technology for supply management may lead manufacturers or distributors to reduce the size of their inventories. This minimizes product loss from short expiration times and carrying costs. However, smaller inventories mean that there are fewer reserves available to respond in the event of production problems. Overall, it does appear that inventories are smaller due to a shift to "just in time" production, and that leaves little leeway for even small changes in supply.

Some reports in the media about drug shortages have focused on the lack of raw materials necessary to manufacture certain classes of drugs that are currently experiencing shortages. In the past, some shortages of drugs have been due to shortages of underlying raw materials, particularly of the active pharmaceutical ingredient (API) for a specific drug. However, this does not appear to be a significant contributor to the current shortages of sterile injectables. In fact, in 2010 and 2011, drug manufacturers cited unavailable API as the primary cause in less than 10 percent of drug shortage situations.

Actions to Prevent or Mitigate Shortages

In 1999, FDA formed the Drug Shortage Program (DSP) within CDER in an effort to begin monitoring and mitigating the impact of drug shortages. DSP facilitates the prevention and resolution of shortage issues by collaborating with FDA experts, industry, and other external stakeholders. In addition, DSP provides information about drug shortages to the public, health care professional organizations, patient groups, and other stakeholders.

When FDA becomes aware of a potential drug shortage, either from pharmacists, physicians, pharmacy organizations, manufacturers or other sources, the Agency works collaboratively with the affected firm or firms to return the product to its usual market availability as quickly and as safely as possible, while helping prevent any harm to patients. Although FDA cannot require firms to continue production of a product or increase production in response to a shortage, it does encourage other firms that make the drug to ramp up production, if they are willing and able to do so. FDA also expedites the review of submissions from manufacturers that may alleviate the drug shortage, which may include requests from existing manufacturers to extend the expiration date of products, make manufacturing changes to increase capacity, use a new raw material source, or change product specifications, as well as applications from new manufacturers who may be willing to enter the market to address a shortage situation. When a shortage is caused by manufacturing and quality problems, FDA works directly with the affected firm to develop short and long-term solutions to the problems. FDA can also use its regulatory discretion for a manufacturer to continue marketing a medically necessary drug, if the manufacturer can develop a method to resolve a quality issue prior to the drug's administration.

FDA carefully considers the impact of any drug shortage on patient care and access before taking any enforcement action. One example of a situation in which FDA worked closely with a manufacturer to address a quality concern was the case of the shortage of the drug cytarabine, a sterile injectable drug that is used to treat certain types of leukemia. Beginning in 2010, a manufacturing change led to crystal formation in the vials of cytarabine, which poses an extremely dangerous situation to patients. FDA worked with the manufacturer and found that if the vials were warmed, the crystals would dissolve and the danger to patients would be mitigated. Utilizing our regulatory discretion, FDA permitted the manufacturer to ship the vials with a letter to health care professionals, notifying them to inspect for crystal formation and, if

present, to warm the vials to dissolve crystals to ensure patient safety. The use of regulatory discretion helped alleviate this critical shortage temporarily until the manufacturer was able to determine the cause and resolve the crystal formation problem.

In other cases, FDA has been able to mitigate potential shortages due to the discovery of metal shavings and other foreign particles in injectable drug products. A recent example was sodium phosphate, which is a medically necessary electrolyte needed for IV nutrition in critically ill patients. In early 2011, the manufacturer found foreign particles in the drug product, posing a significant safety concern to patients. After the manufacturer generated data showing the particles could successfully be removed with a filter and with that process the drug could be used safely, FDA exercised regulatory discretion for the drug to be shipped with a letter to notify health care professionals that the filter needed to be used with the drug. This allowed the drug to be available for patients while the firm addressed the particulate issue for future production and averted the risk to patients of having particulate matter injected into their veins.

FDA can also use its regulatory discretion with regard to the temporary import of non-FDA-approved versions of critical drugs, when a shortage cannot be resolved immediately. However, there are several factors that limit the applicability of this option. The product may already be in shortage abroad, which may hamper our ability to alleviate the problem in the United States. In addition, although there may be foreign suppliers that possess or have access to a particular drug, these suppliers are not necessarily FDA-approved and may need to be inspected, and their drug labels evaluated, before a product can be imported into the United States. Once a foreign firm is identified as willing and able to supply the drug, FDA can exercise enforcement discretion for the temporary import of a foreign drug after ensuring there are no significant safety or efficacy risks for U.S. patients. The temporary importation is tightly controlled and distribution is closely

monitored. For example, FDA must ensure that drugs imported from abroad are manufactured in a facility that meets FDA quality standards. FDA will then post information about the imported drug on the drug shortage website.[7] FDA has done this for the import of a number of critical drugs during a shortage, including: propofol, Foscarnet, ethiodol, thiotepa, norepinephrine, Xeloda, leucovorin and levoleucovorin.

As noted above, FDA does not have the statutory authority to require firms to continue production if they decide to stop, or require other firms to increase production in response to a shortage. Firms are statutorily required to provide FDA with notice of manufacturing discontinuations only in limited circumstances, and FDA lacks explicit authority to impose penalties on firms that do not submit required reports of discontinuations. Prompt notification is important for all disruptions in supply that could lead to shortages. Early notification leads to a better chance of timely resolution. In 2010, FDA was able to prevent 38 drug shortages due to early voluntary notification from firms, and in 2011, FDA has prevented 195 drug shortages as a result of voluntary notification and close collaboration with manufacturers to avert shortage situations.

Recent Efforts to Further Reduce and Prevent Drug Shortages

Although our work has enabled the Agency to successfully prevent 233 shortages since the beginning of 2010, drug shortages are on the rise. In response to this growing problem, the Administration has taken several recent actions to better understand and respond to drug shortages.

[7] *http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050792.htm.*

In July of this year, Dr. Howard Koh, Assistant Secretary for Health at the Department of Health and Human Services (HHS or the Department), convened a series of meetings with representatives from across the Department to find out more about the root cause of shortages and what steps could be taken within existing authorities to decrease the frequency of shortages in the future.

On September 26, 2011, FDA hosted a public meeting to gain additional insight into the causes and impacts of drug shortages, and possible strategies for preventing or mitigating drug shortages. Interested parties who attended included professional societies, patient advocates, industry, researchers, pharmacists, and other health care professionals. A docket has been opened in relation to the public workshop where comments can be received from the public.[8]

On October 31, 2011, the Administration took a series of steps to reduce drug shortages. This included the issuance of an Executive Order by the President,[9] which directed FDA, in cooperation with the Department of Justice, to take action to help further reduce and prevent drug shortages, protect consumers, and prevent price gouging. In an effort to encourage broader reporting of manufacturing discontinuances, the President's order directs FDA to use all appropriate administrative tools to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life-supporting or life-sustaining, or that prevent debilitating disease. The Executive Order also requires FDA to expand its current efforts to expedite review of new manufacturing sites, drug suppliers, and manufacturing changes to help prevent shortages. Under the President's Order, FDA is also directed to work with the Department of Justice to examine whether secondary

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[8] Drug Shortage Docket website: *http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0690-0001.*
[9] *http://www.whitehouse.gov/the-press-office/2011/10/31/executive-order-reducing-prescription-drug-shortages*

wholesalers or other market participants have responded to potential drug shortages by hoarding medications or raising prices to gouge consumers, and whether these actions are consistent with applicable laws.

On the same day the President signed the Executive Order, the Administration announced its support for bipartisan legislation (S. 296 and H.R. 2245)[10] that would require all prescription drug shortages to be reported to FDA and would give FDA new authority to enforce these requirements. The Administration also announced that, over the coming weeks, FDA would provide additional staffing resources to enhance the Agency's ability to prevent and mitigate drug shortages. HHS released a report, prepared by the Office of the Assistant Secretary for Planning and Evaluation (ASPE), which is detailed further in their testimony today. Additionally, FDA released a report entitled "A Review of FDA's Approach to Medical Product Shortages"[11] on its role in monitoring, preventing, and mitigating drug shortages, which included recommendations to further reduce the impact of these shortages.

In addition, FDA sent a letter to pharmaceutical manufacturers,[12] reminding them of their current legal obligations to report certain discontinuances to the Agency, and urging them to voluntarily notify FDA of all potential disruptions of the prescription drug supply to the U.S. market, even where disclosure is not currently required by law. The letters to manufacturers and the Executive Order have produced a significant increase in the number of potential shortages reported to FDA. In the 10 months preceding the Administration's actions (January through October 2011), the Agency received an average of approximately 10 notifications per month. In the four weeks

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[10] Press Release: *http://www.whitehouse.gov/the-press-office/2011/10/31/we-can-t-wait-obama-administration-takes-action-reduce-prescription-drug.*
[11] *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm275051.htm.*
[12] *http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm277675.htm.*

following the letters to the manufacturers and issuance of the Executive Order, we received 61 notifications, a six-fold increase.

Other recent activities FDA has been working on to help prevent or mitigate drug shortages include:

- Doubling the number of staff in the Center to assist in coordination and response activities, as well as expediting actions (e.g., inspections) that would help to alleviate drug shortages;
- Developing several guidances for industry on reporting product disruptions, supply interruptions, and potential shortages;
- Meeting with various stakeholders to discuss shared opportunities to prevent and mitigate shortages, including; the Generic Pharmaceutical Association, the Pharmaceutical Research and Manufacturers of America, the Biotechnology Industry Organization and drug wholesalers;
- Exploring options for improving the drug shortage database for the internal tracking of shortages, as well as utilizing the database to develop prediction models for drug shortages;
- Assessing commercial systems that could be contracted to provide ongoing or periodic data on sales and distribution of drugs at the wholesale level to detect early signals of potential shortages or supply disruptions;
- Working with the Department of Justice, as directed in the Executive Order, regarding issues related to price gouging and hoarding, including reports from pharmacists and other health care providers in connection with drug shortages;

- Announcing a public meeting on proposed recommendations for establishing a generic drug user fee. The primary goal of this user fee program is to bring median time to approval from around 30 months to a primary review goal of 10 months. This will bring generics to market faster, which should help alleviate shortages. In addition, FDA will continue to prioritize review of generic applications for products that are in shortage situations.

CONCLUSION

FDA and the Administration are committed to addressing the important issue of drug shortages. FDA is doing everything it can under its current administrative authority to help prevent and mitigate drug shortages. As noted previously, there has been a significant increase in the number of notifications as a result of the letters to manufacturers and the Executive Order, which will continue to help mitigate a substantial number of drug shortages. It is our goal to continue a healthy and substantive dialogue with all interested stakeholders, both internally and externally, as we seek a solution to the problem of drug shortages. This is a challenge that we must work collaboratively to solve. FDA has taken a number of important steps and will continue to work with industry, providers and patients to address this issue. We also recognize the important role that you and other members of Congress play, and we welcome the opportunity to discuss this important topic with you both today and moving forward.