TESTIMONY OF

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"EXAMINING THE INCREASE IN DRUG SHORTAGES"

SUBCOMMITTEE ON HEALTH

ENERGY & COMMERCE COMMITTEE

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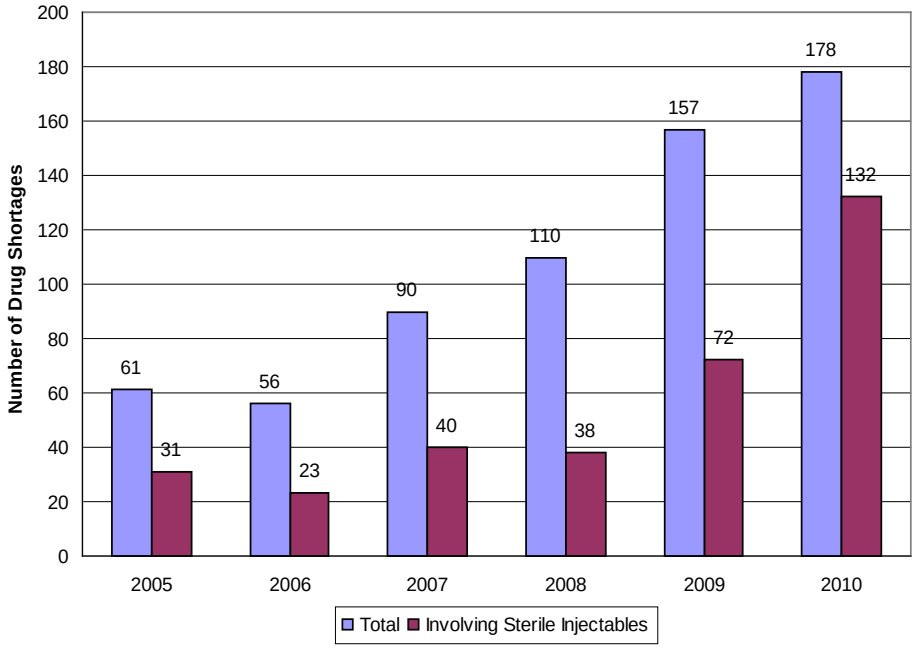
Good Morning, Chairman Pitts, Ranking Member Pallone and distinguished members of the Committee. I am Dr. Howard K. Koh, the Assistant Secretary for Health at the United States Department of Health and Human Services. Thank you for inviting me here today to discuss the growing problem of drug shortages. This is a very troubling situation, and one that the Department, and the Secretary herself, take very seriously. The increasing number of drug shortages has the potential to have an impact on our entire health care system. But, as we discuss and debate this problem, we should bear in mind that the people affected most by these shortages are patients and their families. Although many of the root causes of drug shortages lie outside our purview, we at the Department are committed to confronting this problem, and are eager to work with others to help find substantive long-term, as well as short-term, solutions to the challenge of drug shortages.

OVERVIEW: THE SCOPE OF THE DRUG SHORTAGE PROBLEM AND POTENTIAL UNDERLYING CAUSES

The Food and Drug Administration (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 at the patient level.

According to FDA's Center for Drug Evaluation and Research (CDER), the number of drug shortages has been rising steadily over the last five years. While there were only 61 shortages reported by CDER in 2005, in 2010 there were 178. This trend has continued into 2011 with an even greater number of drug shortages. Although shortages can occur with any drug, shortages of generic sterile injectables currently make up a large and increasing share of these shortages, despite the fact that generic 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. Oncology drugs account for 28 percent of shortages followed by antibiotics at 13 percent. During 2010 and 2011, 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.

Figure 1: Number of US Drug Shortages Addressed by the Drug Shortage Program, 2005-2010



(Source: CDER Drug Shortage Program)

Figure 1 above shows the trend over the past six years in the total number of drug shortages as reported to the FDA, and the relative number of shortages attributable to sterile injectables. In 2010, 74 percent of the shortages involved older sterile injectables, and approximately 54 percent of these were due to product quality issues such as particulates, microbial contamination, impurities and stability changes resulting in crystallization. Approximately 21 percent of the shortages were due to production delays and capacity issues and 11 percent were due to manufacturer discontinuations, usually for business reasons. Some of the other trends that were seen to a lesser extent were raw material issues, increases in demand due to another shortage, loss of a manufacturing site and component problems.

There is no single reason that drug shortages occur. HHS has developed a number of hypotheses for the 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, changes to inventory and distribution practices, difficulty in producing a given drug, quality and manufacturing problems, production

delays, discontinuations for business reasons, and unanticipated increased demand. The majority of drug shortages occur with generic drugs (often ones that have been on the market for decades). The profit margins on generic drugs are quite small compared with brand name drugs, and over time, some companies may choose to discontinue production of generic drugs due to lack of profitability.

Classical economic theory suggests that a drug shortage should be corrected by the laws of supply and demand. However, drug markets do not operate according to these principles in every instance. A declining supply of a drug does not necessarily result in a price increase, and increased drug production to fill the shortage gap. Part of the reason for this is that the vast majority of drug prices are established in contracts and not subject to short-term fluctuations. Additionally, pharmacy benefit managers and other drug purchasers are ordering such large quantities of drugs, that they have the power to put downward pressure on drug prices. Finally, when a shortage does occur, the ability to expand revenues by either expanding sales or raising the drug price may be insufficient for existing producers to make the necessary capital investment to expand production, or for new companies to enter the market.

Industry consolidation has also contributed to the drug shortage problem. A majority of the injectable drugs classified as experiencing a shortage are produced by only seven manufacturers. Generally, when a firm has a manufacturing or quality problem they will often 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 entail a much more complex manufacturing process than solid dosage forms. Consolidation has led to fewer firms making these drugs and the firms have a limited number of manufacturing lines. When one firm experiences a quality problem which results in production holds or slowdowns, the remaining firms are usually not able to make up the shortfall due to capacity constraints.

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 non-controlled substance 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 both 2010 and 2011, unavailable API was cited by drug manufacturers as a factor in less than 10 percent of shortages.

Changes in 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.

Even if long-term manufacturing capacity is sufficient to meet demand, the difficulty of producing some types of drugs and drug manufacturing problems may lead to sporadic shortages in the short-term. As previously noted, there has been an increasing number of serious manufacturing and quality problems with sterile injectable drugs. These drugs are complex to manufacture because special techniques and processes are used to maintain sterility so the product is not contaminated. When quality or manufacturing problems are discovered by the company or healthcare providers and reported to FDA or are found by FDA upon inspection, FDA works closely with the company to address any risks involved to help prevent harm to patients. FDA also considers the impact a shortage would have on patient care and access before taking any enforcement action.

FDA ACTIONS TO PREVENT OR ALLEVIATE SHORTAGES

The impact of drug shortages on patients can be significant and even life-threatening. Certain drugs that have recently been in shortage, such as "crash cart" drugs, can literally be life-saving in the acute setting, while others, such as outpatient chemotherapy drugs, must be administered

within days or weeks in order to provide maximum benefit. Shortages of these drugs not only have an impact upon clinical decision-making, but they could also significantly affect patient outcomes. For example, a shortage of generic propofol 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. FDA's awareness of these consequences drives efforts to prevent and resolve shortages as soon as possible.

In 1999, FDA formed the Drug Shortage Program (DSP) within CDER in an effort to begin monitoring and mitigating the impact of potential and actual 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, healthcare professional organizations, patient groups and other stakeholders.

When FDA becomes aware of a potential drug shortage, the Agency works collaboratively with the affected firm(s) 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 to do so. FDA also expedites the review of submissions from manufacturers which may include requests to extend the expiration date of products, increase capacity, use a new raw material source, license new manufacturers, and permit changes in product specifications. For manufacturing and quality problems, FDA works with the firm to address the issues. Problems that require intervention may pose very low risk (e.g. wrong expiration date on package) or high risk (particulate in product or sterility issues) to patients. In addition, FDA may also use flexibility and discretion to alleviate shortages while mitigating any significant risk to patients.

Through the actions of the FDA working with the manufacturer, shortages are often mitigated. One notable example involves the treatment for leukemia. In this recent case there was a shortage of the drug cytarabine (used to treat certain types of leukemia) which resulted from

crystal formation in the vials, FDA worked with the manufacturer and found that if the vials were warmed the crystals would dissolve and the danger to patients was mitigated. The manufacturer was then able to ship the vials with a letter to healthcare professionals notifying them to inspect for crystal formation and if present, to warm the vials to dissolve crystals to ensure patient safety.

In another case, FDA was able to mitigate a shortage by allowing the use of a filter to safely remove foreign particles contained within vials of injectable drugs, averting the obvious risk to patients of having metal shavings or other particulate matter injected into their veins. If the firm can provide data to FDA showing that the particles can be safely filtered out of the drug without impacting the drug's effectiveness, FDA can prevent a shortage using enforcement discretion to allow the drug to be shipped with the necessary filter until the firm is able to correct the problem for future production. A recent example was sodium phosphate, which is a medically necessary electrolyte needed for IV nutrition in critically ill patients. The firm found particles in the drug product, which is a significant safety concern. The manufacturer was able to generate data showing the particles could successfully be removed with a filter and the drug was shipped with a letter to notify healthcare 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 it represents a success story in the collaboration between FDA and companies in addressing drug shortages.

FDA can also use its regulatory enforcement 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, and importation to the United States could exacerbate the shortage. In addition, while 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 exercises enforcement discretion for the temporary import of a foreign drug after ensuring there are no significant safety or efficacy risks for U.S. patients. 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. 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. All of this is necessary to ensure that the non-FDA approved version is safe for U.S. patients.

Currently, companies voluntarily provide much of the drug shortage information posted on FDA's website. FDA staff work very closely with firms to address the issues that led to the shortages and work with manufacturers to fill the market void. The Agency also works to communicate information about shortages to the public and stakeholders based on information provided by manufacturers.

As noted above, FDA does not have the statutory authority to require a firm to continue production if they decide to stop, nor are firms required to increase production in response to a shortage. Firms are not required to provide notice of discontinuations (except for some sole-source medically necessary products), nor does FDA have explicit authority to impose a penalty on firms that do not submit required reports of discontinuations to FDA. Notification is important for all discontinuations or disruptions that could lead to shortage issues and not just for sole source drug products. It is helpful when manufactures report to FDA any disruption or discontinuation that could lead to potential shortages as soon as it is known. Early notification leads to a better chance of timely resolution. Although FDA does not have explicit authority to require a firm to notify the Agency of shortages, such authority may enable FDA to help prevent or mitigate more potential drug shortages.

In 2010 FDA was able to prevent 38 drug shortages i due to early voluntary notification from firms and thus far in 2011, FDA has already prevented 99 drug shortages.

THE IMPACT OF DRUG SHORTAGES ON MEDICAL RESEARCH

The Department is concerned about the market impact of drug shortages on patients and their health care providers. Drug shortages can result in operational difficulty and strain for medical

studies and clinical trials sponsored by the National Institutes of Health (NIH) within HHS. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. NIH conducts approximately 630 intramural clinical trials on its Bethesda, Maryland campus and extramurally funds about 5,100 clinical trials at research institutions across the country. As I outline below, drug shortages create significant difficulty and disruptions for medical researchers and the patients they treat.

National Cancer Institute (NCI)

Shortages of cancer drugs are having an impact on studies sponsored by the NIH National Cancer Institute (NCI). While there have been periodic shortages of different cancer drugs over the past several years, nothing to date has approached the scale of the current shortages of chemotherapy drugs. We are now facing shortages of several generic cancer drugs that are widely used in treatment and are essential for clinical research. These drugs include standard therapies for the treatment of lung, breast, ovarian, testicular, and colorectal cancers, as well as several types of lymphomas and leukemias.

Many of the cancer drugs in short supply – including doxorubicin, daunorubicin, 5-FU, paclitaxel, bleomycin, and cytarabine – are mainstays of the anti-cancer arsenal, and were largely developed through federally-funded research begun 20, 30, even 40 years ago. They are still essential to treatment and research: the NCI currently is sponsoring 96 clinical trials that include combination or control arm drug regimens that require a supply of doxorubicin; 13 trials that require daunorubicin; 69 trials that require 5-FU; 108 that require paclitaxel; 8 that require bleomycin, and 55 that require cytarabine. [1] Taken together, these studies represent thousands of patients, as well as a significant federal investment in clinical trials research. 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. In some cases, patients are either foregoing treatment entirely, or receiving suboptimal therapies.

National Institute of Allergy and Infectious Diseases (NIAID)

Drug shortages have also been a major issue for the NIAID-supported AIDS Clinical Trial for its randomized trial comparing three different regimens of chemotherapy, each used in combination with compatible antiretroviral therapy, for the treatment of advanced AIDS-related Kaposi Sarcoma. Due to shortages of liposomal doxorubicin (Doxil), and generic vincristine and bleomycin, the trial will likely be on hold for at least a year. There is also a shortage of intravenous trimethoprim-sulfamethoxazole, the first-line antibiotic therapy used to treat *Pneumocystis carinii* infection, a potentially life-threatening condition in individuals with HIV/AIDS, affecting the care of patients enrolled in NIAID intramural research protocols.

HHS ACTIONS AND ACTIVITIES

As noted above, FDA has been actively engaged in tracking shortages and using existing authorities and mechanisms to work with the industry to prevent shortages from occurring, or to mitigate their impact when they do occur. In 2010, 38 drug shortages were prevented through the actions of FDA collaborating with drug sponsors, and in 2011 99 drug shortages have been prevented.

However, drug shortages continue to be a pressing public health problem. The Department has taken a number of steps to determine the extent of the problem, and to identify the best course of action for addressing the drug shortage problem.

In July of this year, I convened a series of meetings with representatives from across the Department to find out more about what is at the root of shortages, and what steps could be taken within existing authorities to decrease the frequency of shortages in the future. At these meetings were HHS representatives from FDA, NCI, CDC, the office of the Assistant Secretary for Preparedness and Response, Assistant Secretary for Planning and Evaluation and the Centers for Medicare and Medicaid Services, among others. The initial discussions were heavily focused on gaining a better understanding of the situation as it currently exists, as well as brainstorming about possible solutions. These have been productive meetings and are ongoing. We continue to

look for ways to collaborate within the Department to combine our collective experience and expertise to find workable solutions.

All parties involved in the supply of drugs to Americans have a responsibility to make sure patients have access to the drugs they need. To gain this perspective, the Secretary and the Department have engaged important external stakeholders to hear their individual views on the issue of drug shortages. Earlier this month, the Secretary, along with other senior leaders in the Department, hosted a meeting with over a dozen representatives from pharmaceutical manufacturers, professional medical organizations, hospitals, insurance companies, group purchasing entities and patient advocacy organizations. This meeting gave us firsthand insight to the challenges stakeholders face, as well as provided us with ideas about possible opportunities for collaboration and further discussions with these organizations as we work to address shortages.

In addition, FDA will be hosting a public meeting to discuss drug shortages on September 26. This meeting is being held to gain additional insight about the causes and impact of drug shortages, and possible strategies for preventing or mitigating drug shortages from all interested parties, including: professional societies, patient advocates, industry, researchers, pharmacists and other healthcare professionals.

Following this public meeting and consideration of the various comments, FDA will release a report which reflects the important analysis of the problem and recommendations with respect to its role. Potential solutions are also being rigorously examined. One suggestion is a mechanism for manufacturers to report impending supply disruptions and discontinuation of drugs, which could help to curb drug shortages and improve the continuity of the drug supply. The sooner FDA learns of a drug shortage, the more effective it can be in helping to notify providers and minimizing the impact on patients.

Meanwhile, the FDA will continue its efforts to work with manufacturers to mitigate shortages. For example, FDA already expedites requests to qualify new manufacturing sites, new production lines or new raw material suppliers to avert drug shortages. HHS remains committed

to working with manufacturers, providers, patient advocates, and other stakeholders to help minimize drug shortages, protect patients, and identify solutions to this serious problem.

CONCLUSION

The Department is committed to addressing the important issue of drug shortages. It is our goal to continue a healthy and substantive dialog 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. 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.