EXAMINING THE INCREASE IN DRUG SHORTAGES

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED TWELFTH CONGRESS

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C O N T E N T S

EXAMINING THE INCREASE IN DRUG SHORTAGES

FRIDAY, SEPTEMBER 23, 2011

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

The subcommittee met, pursuant to call, at 9:36 a.m., in room 2322 of the Rayburn House Office Building, Hon. Joseph Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Shimkus, Myrick, Murphy, Blackburn, Gingrey, Lance, Cassidy, Guthrie, Walden, Pallone, Dingell, Schakowsky, Matheson, DeGette, and Waxman (ex officio).

Staff present: Clay Alspach, Counsel, Health; Ray Baum, Senior Policy Advisory/Director of Coalitions; Marty Dannenfelser, Senior Advisor, Health Policy and Coalitions; Andy Duberstein, Special Assistant to Chairman Upton; Debbee Keller, Press Secretary; Jeff Mortier, Professional Staff Member; Katie Novaria, Legislative Clerk; John O'Shea, Professional Staff Member, Health; Chris Sarley, Policy Coordinator, Environment and Economy; Alan Slobodin, Deputy Chief Counsel, Oversight; Heidi Stirrup, Health Policy Coordinator; John Stone, Associate Counsel; Phil Barnett, Democratic Staff Director; Stephen Cha, Democratic Senior Professional Staff Member; Alli Corr, Democratic Policy Analyst; Eric Flamm, FDA Detailee; Ruth Katz, Democratic Chief Public Health Counsel; Elizabeth Letter, Democratic Assistant Press Secretary; and Karen Lightfoot, Democratic Communications Director and Senior Policy Advisor.

Mr. PITTS. This subcommittee will come to order. The chair recognizes himself for 5 minutes for an opening statement.

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

In 2005, 61 drug shortages were reported to FDA. By 2010, there were 178 reported drug shortages, 132 of which involved sterile injectable drugs. So far this year, FDA has continued to see an increasing number of shortages, especially those involving older sterile injectable drugs. These shortages have involved cancer drugs, anesthetics used for patients undergoing surgery, as well as drugs needed for emergency medicine, and electrolytes needed for patients on IV feeding.

It appears that there are many potential causes of these drug shortages. In some cases, shortages have been caused by quality and manufacturing issues. Additionally, production delays at the manufacturer level, including limited production lines for certain older drugs, and difficulty in receiving raw materials and components from suppliers have caused drug shortages. Many raw material suppliers also experience capacity problems at their facilities, causing delays that ripple through the drug production process.

Shortages can also result from a company discontinuing a particular drug. Certain drugs are susceptible to shortages, particularly those that are complex to manufacture, such as injectable drugs, or require longer lead times. FDA cannot compel a company to manufacture a particular drug, and, if there is a shortage of that drug, it cannot compel other firms to increase their capacity. Further, companies are not required to notify FDA in advance of a potential drug shortage, unless a company is discontinuing a sole source, medically necessary drug. In that case, a company must inform FDA 6 months in advance.

Drug shortages have real effects on real patients. Due to shortages, patients have not received the appropriate drugs for their conditions, often getting a less effective drug or a more costly substitute as a result. According to a study done by Premier Healthcare Alliance of 228 hospitals, retail pharmacies, and other health care facilities, nearly 90 percent of hospitals reported a drug shortage in the last half of last year that may have caused a patient safety issue, resulted in a procedure's delay or cancellation, required a more expensive substitute, or resulted in a pharmacist compounding a drug.

I look forward to hearing from our witnesses today about their experiences with drug shortages and learning what remedies they believe are necessary. I would like to say a special hello to Richard Paoletti, Vice President, Operations; Pharmacy, Laboratory, and Radiology at Lancaster General Hospital in my home district.

Lancaster General is the largest employer in the 16th Congressional District, and, for 10 of the past 13 years, it has been named among the "Top 100 Hospitals in America" by Thomson Reuters, a leading source of healthcare business intelligence. The hospital is also helping to revitalize the northwestern part of Lancaster City through a partnership with Franklin and Marshall College.

Again, thank you to our witnesses, and I will yield the balance of my time to Congressman Shimkus from Illinois.

[The prepared statement of Mr. Pitts follows:]

Rep. Joseph R. Pitts
Opening Statement
Energy and Commerce Subcommittee on Health
Hearing on "Examining the Increase in Drug Shortages"
September 23, 2011
(As Prepared for Delivery)

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OPENING STATEMENT OF HON. JOHN SHIMKUS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Mr. SHIMKUS. Thank you, Mr. Chairman. And we want to welcome our folks at the 2 panels. Obviously, this is of concern. I am a market-based conservative capitalist, and whenever there is a lag in a commodity good or product, you have to really wonder about the demand and the supply and the available cost because when there is limited supply and a high demand, cost should go up.

So that begs a question is, what is constraining the market signals from producing the product that the consumers need? Is that insurance companies? Is that government reimbursement rates? Is that the State Medicaid provisions? That is what I will be looking at because the bigger the government is, the more manipulative it gets in the market services, the less its ability to provide goods and services to consumers.

So we appreciate that and look forward to it, and I yield back my time, Mr. Chairman. Thank you.

Mr. PITTS. The chair thanks the gentleman and recognizes the ranking member of this subcommittee, Mr. Pallone, for 5 minutes.

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

Mr. PALLONE. Thank you, Mr. Chairman. I want to thank you for holding today's hearing on this important issue. I am encouraged by the bipartisan nature of this effort and thank our witnesses for joining us.

Today, we will discuss the recent increase in drug shortages that have been the subject of numerous reports. Drug shortages appear to be on the rise at an alarming rate and are threatening the supply of some of our most important medications from lifesaving oncology drugs to antibiotics that rid us of infection to antiseptics that get us through the most minor surgical procedures. These drugs have become an important part of our healthcare system.

No patient must be told that their chemotherapy must be postponed because the only drug used to treat their type of cancer is unavailable. And likewise, no anesthesiologist wants to begin their workday with the realization that they will have to use subpar drugs on a patient because the one they normally rely on is out of stock indefinitely. So we can't let this become the new norm.

We are dependent upon the medications on the FDA's drug shortage list for years and continue to look for them for our health and wellbeing. It is alarming that drugs that have been around for so long would suddenly be the most difficult to keep hospitals, pharmacies, and doctors' offices supplied with. Furthermore, these drugs tend to be low-cost generics, which are an essential component of healthcare for most Americans as they seek to keep their healthcare costs low.

In this fiscal climate, having a readily accessible supply of generic medication is of profound importance, and to that end, it has been disheartening to learn that the so-called gray market would take advantage of such a dire situation to engage in price-gouging at the expense of those desperate enough to pay.

So I am hoping that we can begin today to identify the cause of these shortages and discuss solutions for replenishing our drug supply. We must address this sudden increase so that Americans can continue to receive high-quality treatments at low cost and remain confident in both the pharmaceutical industry and the healthcare providers.

Unfortunately, companies are not currently required to report to the FDA when a shortage will be occurring whether because of change in investment strategy or manufacturing difficulties, there is currently no policy for notification unless the company is the sole manufacturer.

My colleague, Representative DeGette, has introduced bipartisan legislation, H.R. 2245, the Preserving Access to Life-Saving Medications Act of 2011, as the first step in addressing this issue. This legislation would require manufacturers to notify the FDA of any actual or prospective drug shortages. And I want to commend Representative DeGette on pioneering this effort and hope that as a result of hearing from our witnesses today, we can identify additional solutions to this growing problem.

This hearing will allow us to learn more about why drug shortages are occurring, what the administration and industry are doing to address the problem, and what new authorities the FDA might need to prevent shortages from happening in the future. And I am encouraged that we are exploring this issue in our subcommittee today, look forward to working with you, Chairman Pitts, as you get to the bottom of this issue. And again, thank you for having the hearing.

I yield back.

Mr. PITTS. The chair recognizes the ranking member of the full committee, Mr. Waxman, for 5 minutes.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you, Chairman Pitts, for recognizing me and for holding this hearing.

Recent media and other reports indicate that drug shortages are now at an unprecedented level. Indeed, according to FDA, the number of drugs in short supply in 2010 was almost triple that of 2005. The shortages affect a broad spectrum of critically important drugs—including oncology drugs to treat lymphoma, leukemia, breast and other cancers—and the seizure drugs without which surgeries have to be postponed and antibiotics to remedy life-threatening bacterial infections. Without these drugs, patients' lives are at risk.

Drug scarcities generally affect sterile injectable drugs. These drugs are technically difficult to make and each drug is usually manufactured by only one or a handful of producers. If any one company develops manufacturing problems, which is not uncommon, other companies may have little excess capacity to help fill the need.

With the aging of our population, the outsourcing of drug manufacturing, the increasing consolidation of drug companies, and the general adoption of a just-in-time approach to drug production and

distribution, this problem may be significantly worse unless immediate measures including congressional action are taken to address its multiple causes.

Representative DeGette has introduced legislation that would be an important first step in this process. H.R. 2245, the Preserving Access to Life-Saving Medications Act of 2011, would require manufacturers to notify FDA of any actual or prospective drug shortages. Such advance notice would enable FDA to help avoid or mitigate the shortage by both working with the manufacturer and alerting hospitals and physicians of the problem.

While this is an important piece of legislation that has broad bipartisan support, I don't think anyone believes it alone can solve the drug shortage problem. So I look forward to hearing from our witnesses today to better understand the causes of what is already a crisis for many patients and to find out what we in Congress can do to help prevent shortages in the future. We already had been working in bipartisan manner to learn about this very disturbing issue, and I trust that we will continue to work together to develop and enact legislation to help address it and address it quickly.

Thank you, Mr. Chairman. I yield back the time.

Mr. PITTS. The chair thanks the gentleman. That concludes our opening statements.

Our first panel will be Assistant Secretary for Health at HHS, Mr. Howard Koh. And Mr. Koh, you may begin your testimony. Please summarize in 5 minutes. We will put your entire written testimony in the record. You may begin.

STATEMENT OF HOWARD K. KOH, ASSISTANT SECRETARY OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES; ACCOMPANIED BY SANDRA KWEDER, DEPUTY DIRECTOR, FDA OFFICE OF NEW DRUGS

Mr. KOH. Thank you, Chairman Pitts, Ranking Member Pallone, and distinguished members of the committee. I am Dr. Howard Koh, the Assistant Secretary for Health at the U.S. Department of Health and Human Services. I am very pleased to be joined here by my colleague, Dr. Sandy Kweder, Deputy Director of the FDA Office of New Drugs.

As you already heard, the growing problem with drug shortages is a troubling situation and one that the Department and the Secretary take very seriously. This growing trend has the potential to impact on our entire healthcare system, and as we discuss this problem today, we should always remember that our goal is to protect the health of people affected most by these shortages—patients and their families. And I say that as a physician who has cared for patients for over 30 years.

According to the FDA's Center for Drug Evaluation and Research (CDER), the number of drug shortages has been rising steadily over the last 5 years, as you have already heard. And although shortages can occur with any drug, generic sterile injectables currently make up a large and increasing share. And in fact, in 2010, 74 percent of these shortages involved these older sterile injectable agents. So these include critical products such as oncology drugs, anesthetics, parenteral nutrition drugs, and many drugs used in emergency rooms.

There is no single reason why drug shortages occur so ultimately, in any given situation, many factors are involved and underlying causes they operate either alone or in combination to cause a shortage. These factors include but are not limited to industry consolidation, major issues of quality and manufacturing challenges, changes to inventory and distribution practices, difficulty in producing a given drug, production delays, discontinuations for business reasons, unanticipated increased demand, and shortages of underlying raw materials. These are some of the causes, but more importantly, we the Department are trying to focus now on finding solutions that protect patients.

In 1999, the FDA formed the drug shortage program within CDER in an effort to proactively begin monitoring and mitigating—that is, lessening the impact of—potential and actual drug shortages. And when the FDA becomes aware of any potential shortage, it was collaboratively with the affected firm to return the product to its usual market availability as quickly and as safely as possible while striving to prevent any harm to any patient. Although the FDA cannot require firms to continue production of a product or increase production in response to a shortage, it does encourage other firms to do so.

FDA also expedites the review of submissions from manufacturers, which may include request to extend the expiration date of products, increase capacity, use a new raw material source, license new manufacturers, and prevent changes in product specifications. The FDA is committed to working with drug manufacturers to prevent shortages whenever possible, and in fact, as a direct result of this commitment and the work of the FDA drug shortages staff and experts from across the Agency, last year, 2010, 38 shortages were prevented. And so far for 2011, this year, I am pleased to report for the first time that 99 shortages have been prevented.

Also, at the same time, the FDA goes to great lengths to mitigate shortages—that is, lessening the impact when they occur. One notable recent example involves the well described shortage of the drug cytarabine used to treat certain types of acute leukemia. Crystal formation in the vials of this drug represented a quality and manufacturing problem that led to a disruption in production and a shortage that received tremendous publicity across the Nation within recent months. In this case, the FDA worked with the manufacturer, found that if the vials were warm, the crystals would dissolve and the drug could be then safety administered to the patient, and as a result of this collaboration, the manufacturer was then subsequently able to ship the vials to healthcare professions along with a letter from the FDA notifying them to inspect for crystal formation, and if present, warm the vials to dissolve the crystals. And in this way, the collaboration led to ensuring and upholding patient safety. So as a result of this work, we can report today that this well reported drug shortage has been recently resolved.

In limited circumstances, the FDA can allow the temporary importation of critical drugs when the shortage cannot be resolved immediately. However, there are several factors that limit the applicability of this option. The product may already be in short supply abroad, so importation to the U.S. could exacerbate the shortage.

FDA must also ensure that drugs imported from abroad are manufactured in facilities that meet FDA quality standards.

To discuss these and other possible solutions, the FDA will be hosting a public meeting next Monday, September 26, and this meeting is being held to gain additional insight about causes and impact of this challenge and possible strategies for solutions.

Then on Friday, September 30, the FDA is conducting a webinar for the general public, and this is an opportunity for people to learn more about what the FDA is doing to address this challenge, and it will also be a venue for citizens to ask questions directly to FDA experts who are working on this topic every day.

Although I have focused my comments until now on the FDA, I should stress that the entire Department of Health and Human Services has been fully engaged on this topic for quite some time. We view this as a pressing public health challenge, and we want to resolve this on behalf of the Department and indeed the entire country.

This past summer, I personally convened a series of meetings with representatives from FDA; NCI, our National Cancer Institute; CDC, our Centers for Disease Control and Prevention; the Office of the Assistant Secretary for Preparedness and Respondent; the Office to the Assistant Secretary for Planning of an Evaluation; the Centers for Medicare and Medicaid Services, CMS; and others. We have joined together as one department to explore more deeply the root causes of this problem and the possible steps that can be taken to address them. These have been productive meetings and we pledge to continue them until the problem is solved. We look for as many ways as possible to maximize our efforts within the Department to protect the public health.

Also, earlier this morning, Secretary Sebelius, 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, and this crucial meeting gave us firsthand insight into these challenges, generated a good discussion with the stakeholders, and also served as a foundation for our future collaboration.

Shortly, later on this fall, the FDA will release a report which reflects an even more detailed analysis of the problem and updated recommendations for the future. Potential solutions are being examined. One suggestion is a mechanism for manufacturers to report impending supply disruptions and discontinuation of drugs, which could help to curb shortages and improve the continuity of the drug supply. The sooner the FDA learns of a drug shortage, the more effective they are going to be in helping to notify providers and the public and upholding patients' safety.

So we remain committed to working with all parties—manufacturers, providers, patient advocates, and other stakeholders to help minimize and solve this problem. So in conclusion, the Department is committed to addressing and solving this critical public health challenge. It is our goal to advance this dialogue with all interested parties both internal and external, and we also recognize and deeply respect the important roles of the Members of Congress, and we

welcome the opportunity to discuss this important topic with you today.

So thank you very much, and Dr. Kweder and I will be very happy now to take any questions you may have.

[The prepared statement of Mr. Koh follows:]

TESTIMONY OF

DR. HOWARD K. KOH

ASSISTANT SECRETARY OF HEALTH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

"EXAMINING THE INCREASE IN DRUG SHORTAGES"

SUBCOMMITTEE ON HEALTH

ENERGY & COMMERCE COMMITTEE

U.S. HOUSE OF REPRESENTATIVES

SEPTEMBER 23, 2011

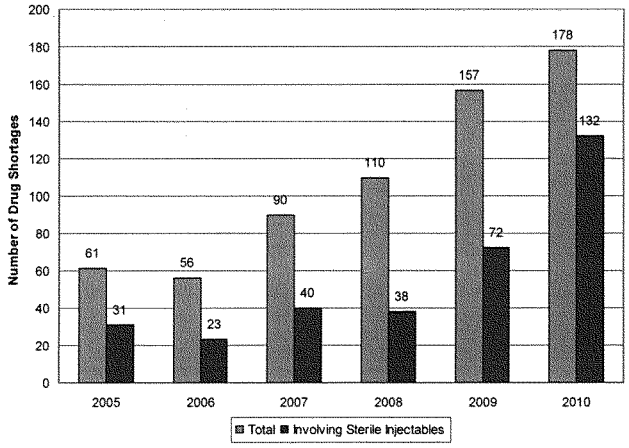
Good Morning, Chairman Pitts, Ranking Member Pallone and distinguished members of the Committee. I am Dr. Howard K. Koh, the Assistant Secretary for Health at the United States Department of Health and Human Services. Thank you for inviting me here today to discuss the growing problem of drug shortages. 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.

Mr. PITTS. The chair thanks the gentleman. Dr. Koh, why have drug shortages increased so much in the last few years?

Mr. KOH. Well, again, there is no one single reason but there are changes here that we are seeing in the backdrop of an economic and business climate that is leading to market consolidation, a complicated manufacturing process that is being conducted increasingly in aging facilities that is leading to quality and manufacturing issues as we have heard now. Sometimes products are discontinued for business reasons. Oftentimes the production of any of these agents is a complicated process. So all these factors converge to create the issue that we are facing right now.

Mr. PITTS. Have other countries experienced shortages such as we have?

Mr. KOH. Unfortunately, the United States is not unique in this situation and yes, we are indeed seeing similar situations in other countries around the world.

Mr. PITTS. And when a shortage occurs in another developing country, how is that situation resolved there?

Mr. KOH. Well, we want to learn more from our colleagues there. I don't know if Dr. Kweder wants to say more about that particular issue.

Ms. KWEDER. We are often contacted by our regulatory colleagues from other countries looking to collaborate on finding solutions to particularly when there are worldwide problems. Different countries have different ways of producing drug, as assuring production of product, but we work as much as possible with others to try and make sure that shortages are limited and mitigated.

Mr. PITTS. Does Europe have a particular method of resolving this situation?

Ms. KWEDER. I believe the method is pretty much similar to ours, particularly since they have multiple countries. They seek other sources of supply from other countries.

Mr. PITTS. And do you know what is causing these drug shortages in these countries in Europe?

Ms. KWEDER. Many of them are the same sorts of things. They are, you know, many of these products are marketed globally. They are not just in the U.S. The sources of the drug substances itself, most of them are foreign sources, so if there is an interruption of a source in the U.S. at a U.S. plant, if a manufacturer in another country has the same source, they will be in the same situation and everyone will be out looking for alternatives at the same time.

Mr. PITTS. OK. Dr. Kweder, what specific steps has the FDA taken to prevent or alleviate drug shortages?

Ms. KWEDER. First, we tend to learn in terms of preventing drug shortages. When companies let us know that they are experiencing a problem, it is usually a problem in production. Sometimes it is a business decision to discontinue a product. When they inform us in advance that that is the case, we work very closely with them to understand the problem and assess whether this shortage would be something that would be critical for patients.

So, for example, if a company is making a product that 20 other companies make, that is not likely to be a critical public health situation. But particularly for these sterile injectables, that is usually not the case. So we will work with a company to help them develop

solutions to fix the problem and avoid an interruption in production. That is not always possible. It is just simply not always possible.

When it is not possible and it looks like the company may have to interrupt production, we go to other manufacturers and we talk to them about their capacity to increase their production. They usually can't turn that around on a dime, but we work with them to facilitate ramping up in order to supply the market with usual sources.

In the original company that is having a problem, we have a number of tools in our kit that we can use to help them address the problem. Dr. Koh gave you an example of the kinds of things that we can do in some cases, you know, to look at the end product itself if there is a problem with the end product itself. In that case it was crystallization of the actual active drug. And we worked with the company. They got right on the case to figure out why those crystals were forming, what could be done to mitigate that, inform providers, and since then, the crystal problem has been fixed.

Mr. PITTS. Do you feel you need earlier warning than you currently have?

Ms. KWEDER. We can always use earlier notification. There certainly are circumstances where things happen very, very unexpectedly. But the majority of cases of shortages, we could have been notified, and in the majority of cases, we are not notified in advance. It is getting better. I will say it is getting better, but we still have a large percentage of actual shortages where we were not aware that it was coming.

Mr. PITTS. Thank you. My time has expired.

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

Mr. PALLONE. Thank you, Mr. Chairman. I would like to initially ask unanimous consent to enter into the record the testimony of the National Coalition for Cancer Research. I think you have a copy of it.

Mr. PITTS. Without objection, so ordered.

[The information follows:]

THE NATIONAL COALITION FOR CANCER RESEARCH

Member Organizations

American Childhood Cancer Organization

American Association for Cancer Research

American Cancer Society Cancer Action Network

American College of Radiation

American Society for Therapeutic Radiology and Oncology

American Society of Clinical Oncology

American Society of Hematology

Association of American Cancer Institutes

Cancer Research and Prevention Foundation

Cancer Treatment Research Foundation

Coalition of Cancer Cooperative Groups

CureSearch National Childhood Cancer Foundation

International Cancer Advocacy Network

International Myeloma Foundation

Kidney Cancer Association

The Leukemia and Lymphoma Society

The Lustgarten Foundation for Pancreatic Cancer Research

Melanoma Research Alliance

Oncology Nursing Society

Pancreatic Cancer Action Network PanCAN

Prostate Cancer Foundation

Society of Nuclear Medicine

The Society of Gynecologic Oncologists

The V Foundation for Cancer Research

Testimony of the National Coalition for Cancer Research
House Committee on Energy and Commerce Health Subcommittee Hearing:
"Examining the Increase in Drug Shortages."

September 23, 2011

The National Coalition for Cancer Research commends the House Committee on Energy and Commerce Health Subcommittee for holding this important hearing to address the severe drug shortage issue that is significantly impacting cancer research and care.

The National Coalition for Cancer Research is a nonprofit coalition of 24 national cancer research, cancer care and patient organizations representing cancer patients and survivors, children with cancer and their families, cancer researchers, nurses and physicians, and cancer hospitals, centers, clinics and specialized research institutions. The organization directs its efforts at making widely known the value of cancer research and the major contributions the National Cancer Program has made to the biomedical sciences and related fields, patient care, to the reduction of cancer incidence, morbidity and death, and issues faced by cancer survivors.

Drug Shortages Impacting Cancer Clinical Trials

According to the University of Utah Drug Information Service, there were 211 reported drug shortages for calendar year 2010. Already this year, there have been 198 reported drug shortages as of August 25, 2011, suggesting that shortages are continuing to increase. If the current trend continues, it is estimated that more than 300 drugs will be in short supply by the end of 2011, an increase of approximately one-third.

The shortage of some cancer drugs is not just affecting patients currently undergoing treatment, but it is also having a significant negative impact on current and future cancer clinical trials. Of the drugs on the most current shortage list, 22 are cancer agents. Of the 22 cancer agents on the drug shortage list, 15 are urgently needed for clinical research purposes.

This impact on cancer research is largely due to the fact that placebos (sugar pills) are rarely used in cancer clinical trials, and are never used alone if an acceptable treatment is available. Therefore, cancer clinical trials are traditionally designed to test the safety and efficacy of the standard of care against, or in combination with, a new treatment being investigated. When the drug that is the standard of care is in short supply or is no longer being manufactured, it severely compromises high priority clinical trials.

These shortages have resulted in important cancer clinical trials being delayed, suspended and/or halting the accrual of new patients into them. Halting a trial wastes the investment made in the treatment, data management and time investment by the patients and clinical scientists participating in the study and

causes the loss of valuable information. In some cases, clinical trial sponsors have been placed in the difficult position of, when permitted, utilizing alternative regimens that are not part of the original protocol due to a shortage of the existing drug being used as part of the investigation. For some clinical trials, particularly those with FDA registration implications and requirements, substitutions of drugs used in the trial are not permitted.

Furthermore, as patients are recruited for clinical research trials with the intent to receive an investigational therapy, the treatment described in the consent form details both the benefits, side effects, and other standard of care treatment options. It is concerning that a patient who opts to receive an investigational treatment in combination with an existing drug, which is short supply, could have instead elected to receive alternative, standard treatment – perhaps in a more timely way. Treatment delays of days to months are critical in the life of a cancer patient and could limit their chances for a cure or remission of their disease.

Another residual impact of drug shortages is the delay in obtaining the data necessary to bring new cancer therapeutics to patients. With more than 400 cancer agents in various stages of development, it is imperative that cancer clinical trials continue uninterrupted in order to obtain the necessary data to seek approval of new anti-cancer drugs as soon as possible.

Following are examples of the impact the current drug shortages are having on cancer clinical trials:

- According to the Coalition of Cancer Cooperative Groups, approximately half of all active cooperative group cancer clinical trials have at least one drug on the shortages list.
- Cooperative Group research sites report they are unable to enroll patients in certain clinical trials, even though the patients meet protocol eligibility requirements, due to the lack of an existing cancer drug being used in the clinical trial.
- Due to a shortage of the drug doxorubicin, two important clinical trials have been delayed. These clinical trials were designed to test this drug in combination with novel agents in patients with Advanced Recurrent Epithelial Ovarian Cancer and those with Hepatocellular Carcinoma of the liver, which is one of the most common tumors in the world and is a leading cause of cancer deaths.
- A shortage of the drug paclitaxel has resulted in delaying the enrollment of eligible lung cancer patients into clinical trials. Furthermore, the shortage of paclitaxel may result in current clinical trial participants being removed from the study.
- Daunorubicin is a chemotherapy treatment for children and adults with Acute Lymphoblastic Leukemia and Acute Myelogenous Leukemia. In one adult trial, a comprehensive cancer center in Alabama reported that, although a patient was eligible to participate in a study, they had no daunorubicin at the center. Drug substitutions are not allowed for this study, so they were unable to enroll the patient into the study.
- The Children's Oncology Group reports difficulties in obtaining daunorubcin for its pediatric Acute Lymphoblastic Leukemia studies. In one trial, a substitution is allowed by the National Cancer Institute when no drug is available; however, the substitution is more toxic, resulting in increased risk for patient harm and side effects.

These are but a few examples of how the shortages of existing cancer therapeutics are impacting cancer clinical trials. Additional examples from various parts of the country are provided in the attached supplemental information accompanying this testimony.

This unprecedented drug shortage situation comes at a time when tremendous advances are being made in the treatment of cancer.

- According to the American Cancer Society, the 5-year relative survival rate for all cancers diagnosed between 1999 and 2006 is 68%, up from 50% in 1975-1977.
- The National Cancer Institute estimates that approximately 11.7 million Americans with a history of cancer were alive in January 2007.
- The 5-year relative survival rate for female breast cancer patients has improved from 63% in the early 1960s to 90% today. The survival rate for women diagnosed with localized breast cancer (cancer that has not spread to lymph nodes or other locations outside the breast) is 98%.
- For all childhood cancers combined, the 5-year relative survival rate has improved markedly over the past 30 years, from less than 50% before the 1970s to 80% today.

A robust and sustained cancer clinical trial enterprise is essential if this positive trend in cancer survivorship is to continue, particularly given that there are some forms of cancer for which the five-year survival rate is still below 50%. Addressing the drug shortage issue is a critical component to the continued advances in clinical cancer research and treatment.

We understand and appreciate the complexity of this issue. We are working with our colleagues in the biomedical research and provider communities to identify potential regulatory and legislative solutions to address this ever-growing problem. However, we cannot overemphasize the urgent need for continued bipartisan efforts to act thoughtfully and expeditiously in order to resolve this critical issue.

The National Coalition for Cancer Research looks forward to working with the members of the United States House of Representatives and Senate, the Department of Health and Human Services, the Food and Drug Administration and the biomedical research community to address this urgent matter.

We thank you for the opportunity to provide this testimony for your consideration.

American Association for Cancer Research
American Cancer Society Cancer Action Network
American Childhood Cancer Organization
American College of Radiology
American Society of Clinical Oncology
American Society of Hematology
American Society for Radiation Oncology
Association of American Cancer Institutes
Gateway for Cancer Research
Coalition of Cancer Cooperative Groups
CureSearch Childhood Cancer Foundation
Friends of Cancer Research
International Cancer Advocacy Network
International Myeloma Foundation
Kidney Cancer Association
Leukemia and Lymphoma Society
The Lustgarten Foundation
Melanoma Research Alliance
Oncology Nursing Society
Pancreatic Cancer Action Network
Prevent Cancer Foundation
Prostate Cancer Foundation
Society of Gynecologic Oncologists
V Foundation for Cancer Research

Addendum to testimony of the National Coalition for Cancer Research
House Committee on Energy and Commerce Health Subcommittee Hearing:
"Examining the Increase in Drug Shortages."

September 23, 2011

Following are additional examples of cancer research studies which have been impacted by drug shortages:

- One large phase III trial compares outcomes for **lung cancer patients** given an accepted standard treatment (either carboplatin and paclitaxel or carboplatin, paclitaxel, and bevacizumab) and patients given the same treatment plus an additional drug – cetuximab. A research site in **Lexington, KY** reports not being able to offer participation in this clinical trial because the center cannot guarantee availability of paclitaxel to these patients.

- No daunorubicin in supply at a research site in **Birmingham, Alabama** led to physicians being unable to enroll a patient with **Acute Myeloid Leukemia** in a cooperative group protocol, and there was no substitution allowed.

- Standard initial treatment for **children with Acute Myeloid Leukemia**, which has a survival rate of between 50-60%, involves the drug daunorubicin, which is in short supply.

- A cancer center in **Boston, MA** almost missed an opportunity for one of its patients to participate on the trial due to the shortage of daunorubicin. Fortunately, the patient was randomized to the clofarabine arm of the trial. If the patient had been randomized to the daunorubicin arm, the center may not have been able to keep the patient on study due to the daunorubicin shortage. Until the drug shortage is resolved, the center may not be able to continue to accrue patients onto this trial.

- The same center reports that lack of availability of paclitaxel, one of the drugs used in a clinical trial, has been affected by this drug shortage and substitution for paclitaxel is not allowed for this study. If the paclitaxel supply is expected within three weeks from the planned date of treatment, treatment can be delayed for those three weeks by the participating clinical trial sites. After a three-week delay, participating clinical trial sites are asked to remove patients from the study. **Until the shortage of paclitaxel is resolved, the center may not be able to accrue patients to this trial because of uncertainty over drug supply.**

- Shortage of daunorubicin for a cooperative group are impacting a study testing a new therapy for patients (ages 18-60) with newly diagnosed **Acute Myeloid Leukemia**, as reported by a research site in **Pittsburgh, PA**, where drug has not been available since June 1, 2011.

- A cancer center in **St. Louis, MO** reports that a clinical trial for breast cancer that has had scientific approval for over two months, but **has not begun because the clinical trial involves a study drug in combination with doxorubicin**. Due to the shortage of doxorubicin, the investigator is rewriting the trial protocol to change the doxorubicin to

another drug. This will delay final approval and activation of the study, which delays this treatment option for its patients.

- Due to the national shortage and allocation of doxorubicin, a cancer center in **Tampa, FL** has had to limit accrual to a study involving patients with Advanced Recurrent Epithelial Ovarian Cancer. It has also been extremely difficult to obtain sufficient supplies of doxorubicin for patients that were previously enrolled in the trial prior to the shortage. One of its active patients is currently on the "waiting list" to receive an allocation of the drug.

- The **Albuquerque, NM**, cancer center recently **lost 21 breast cancer patients to accrual** to a cooperative group trial due to the lack of doxorubicin. The trial is exploring improved treatment methods for women with breast cancer who have a high risk of recurrence. This same research site was unable to enroll an additional **19 patients to other trials for breast, melanoma or ovarian cancer** primarily due to the doxorubicin and doxorubicin shortages.

- A research site in **Lombard, IL** reported shortages of 5FU and Taxol. The site had **three patients with stage 3 colon cancer** eligible for a cooperative group study, who were not able to go on protocol due to the shortage of 5FU. In another study involving 5FU a center in **St. Louis, MO** reported a 5FU shortage that impacted one of its active colon trials. The investigator is working on adding language allowing capecitabine to be substituted for 5FU.

- Shortages of Taxol reported by a research site in **Wheeling, WV**, had led to loss of patient accrual to a cooperative group study for **patients with inoperable non-small cell lung cancer**, stage III. The site seeks to ensure that supply will be available prior to placing patients on study, and the pharmacy at the site is advising that it cannot guarantee supply.

- The same location in **Wheeling, WV** reported shortage of Taxol had led to loss of patient accrual in a cooperative group study testing a second line treatment for **patients with metastatic esophageal or GE (gastro-esophageal) junction cancer**. Adenocarcinoma of the esophagus and the gastro-esophageal junction is reportedly one of the fastest rising malignancies.

- Without Taxol, 5FU, or Leucovorin, **many patients have been unable to participate in trials** at a research site in **Columbus, OH**. Access to drug varies with hospitals in this community network, but priority in the shortage is given to the adjuvant patient population. The site is now getting Taxol in but it is not promised to study patients at this time nor can the site assure its physicians that if they start a patient that there will be enough of the drug for the entire treatment plan.

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Mr. PALLONE. Thank you, Mr. Chairman.

Dr. Koh, we all agree that drug shortages are a real problem facing the country and from what I understand, it is actually getting worse. But I guess it is hard to figure out, at least for me, what the cause is and I would like to ask some questions about the root cause of the problem.

The FDA has said that in 2010, last year, over half of the shortages were due to manufacturing and product-quality issues, and I understand I think you mentioned that many or a majority of those are sterile injectable drugs. Why would these drugs be prone to manufacturing and product-quality issues in particular?

Mr. KOH. Well, many of these products are the result of a long production process, and those production processes are now occurring in fewer manufacturing sites because of industry consolidation. There is also aging of the facilities where this work is ongoing. There are business and economic factors in the background that are lowering the profit margin. So oftentimes, businesses will make a decision to perhaps discontinue a particular product for business reasons, and as a result, we are seeing the quality in manufacturing issues, Congressman, that you are referring to.

Some of these quality issues are quite disturbing where we literally are tracking products that have particulate matter, even pieces of glass and pieces of metal in what should be sterile products that are injected into patients. So this is the reason why the FDA continues to uphold this mission of safe and effective drugs, also high-quality drugs in the middle of this challenging environment.

Mr. PALLONE. Now, Teva is on the next panel, but in their written testimony, they state that it takes 2 or 3 years to get FDA approval for a new supplier for ingredients or an alternative manufacturing site. Is that really true? Does it really take 2 or 3 years to get the FDA approval? And why would that be if it is true? And does it take that long if there is a drug shortage issue involved?

Mr. KOH. Well, let me start, and I am sure Dr. Kweder can add. One of the advances of the FDA in this situation is to prioritize generic drug applications, expedite and accelerate approval in every way possible, particularly if the public health is threatened. So there are efforts to try to advance that time frame. That is also the goal of the Generic Drug User Fee Act, which is under review right now. So these are issues that are very important to the FDA and they take it seriously.

Mr. PALLONE. But I mean is that time period that Teva mentioned, would that generally be true and is there any kind of flexibility that you have to expedite review and inspections of new facilities so they could address the shortage when it exists?

Ms. KWEDER. There absolutely is flexibility, and we do that routinely when we are aware that, say, a new facility is needed or a new supplier is needed and when there is a circumstance that might lead to a potential shortage of an important medical product. We do it routinely. We can often turn things around in a matter of weeks.

Mr. PALLONE. But I mean you haven't answered that 2- or 3-year time span.

Ms. KWEDER. Sure, I would be happy to do that. The 2- or 3-year time span is what is being referred to under usual conditions when there is not a shortage situation or not a shortage situation pending.

Mr. PALLONE. But if there is, then you deal with it quicker?

Ms. KWEDER. Absolutely. But even the 2- to 3-year time frame, as Dr. Koh said, we are working and we are happy to see that there has been agreement on generic user fees that will change that and make that a matter of months and not years.

Mr. PALLONE. I mean my concern is, you know, we face these extraordinary fiscal pressures. The House passed budget for FDA contained a 21 percent cut in appropriated funds. I mean is this cut, would that adversely affect your ability to work with companies to avoid or mitigate shortages? And, you know, I know you mentioned generics. Are you negotiating with the generic industry to develop a user fee and can that help prevent or alleviate drug shortages? This is about the funding now.

Ms. KWEDER. We are negotiating and have reached agreement with the generic industry about user fees. And that will be coming up for discussion by yourself, you know, within the next year.

Mr. PALLONE. And what about this House budget cut, the 21 percent?

Ms. KWEDER. There is no question that resources matter and these are not automated processes. They take people with judgment and knowledge and having enough people makes a big difference.

Mr. PALLONE. All right. Thank you very much.

Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman.

And I would like to request the following statements be entered into the record. I think you have copies. The statement of the National Community Pharmacist Association, the letter from the American Society for Hematology to the House Energy and Commerce Subcommittee on Health, and the statement of the Generic Pharmaceutical Association.

Mr. PALLONE. I have no objection, no.

Mr. PITTS. Without objection, so ordered.

[The information follows:]

NCPA
NATIONAL COMMUNITY PHARMACISTS ASSOCIATION

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United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Health

Hearing on "Examining the Increase in Drug Shortages"

September 23, 2011

The National Community Pharmacists Association (NCPA) appreciates this opportunity to provide comments to the Committee regarding the emerging public health issue of drug shortages. NCPA represents America's community pharmacists, including the owners of more than 23,000 community pharmacies, pharmacy franchises and chains. Together, they employ over 300,000 employees including 62,400 pharmacists, and dispense nearly half of the nation's retail prescription medications.

Effect of Drug Shortages on Community Pharmacy and Patients

Shortages of prescription drugs have tripled during the last five years and reports that this trend will only continue upward are alarming and cause for great concern. The reasons for drug shortages are multi-factorial, some of which are unpredictable but others arise due to marketplace dynamics. Unforeseen disruptions in the supply of raw or bulk materials greatly affect the production of medications. However, drug shortages also result from industry consolidation and the emergence of non-traditional distributors. Shortages cause greater stress on the overall health care system. Drug shortages not only compromise the quality and safety of patient care, but can lead to both direct and indirect increased health care costs.

As community pharmacists on the frontlines of health care delivery, our primary goal is to provide timely and continued access for patients to the life-saving medications they need. To date, most prescription drug shortages have had a greater impact on hospital and health system pharmacies, with almost all hospitals reporting at least one drug shortage in the previous six months.[1] However, these shortages are not confined to in-patient needs. Out-patient and ambulatory patients suffer when oral chemotherapy, specialty drugs, and home infusion products, among others, are scarce on the market.

[1] American Hospital Association (AHA) Shortage Survey, July 2011

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Community pharmacies generally acquire their inventory from a primary wholesaler, but also have relationships with other wholesalers as a backup for product out-of-stocks, recall alternatives, weekend deliveries, and other unique items not normally carried by large wholesalers. In the event of a drug shortage, community pharmacies are limited in their options as the last link in the supply chain to obtain the medications in a timely manner. Pharmacies may start by calling near-by competitors, checking with their back-up wholesalers, or back-ordering the drug. Pharmacies that are located near a distribution center may also request to pick up directly from the center.

Lastly, community pharmacists may be able to provide compounded products, depending on the nature of the shortage. In some cases, the raw materials to manufacture a scare product are not available meaning that compounding pharmacies will not be able to supply the needed drug. Compounding pharmacies may be able to provide compounded prescriptions for patients when raw materials are available and they comply with the laws differentiating compounding from manufacturing. Independent community pharmacies can provide valuable services to their patients in times of certain shortages.

Significant cost increases to patients, payers, and pharmacies

The cause of most drug shortages is attributed to quality issues that arise during the manufacturing process. However, marketplace trends such as pharmaceutical industry consolidation and the projected increase in brand products losing their patents within the next 3 to 5 years signal the potential for supply issues and significant price fluctuations.

In order to remain viable, more generic manufacturers are merging, which may result in fewer producers of essential ingredients, slowed production, and increases in pricing due to fewer competitors in the market. This could lead to substantial increases in pharmacy acquisition costs, a major deterrent for access to the medications.

Community pharmacists have always helped their patients decide if a generic drug is safe and appropriate and have higher generic dispensing rates compared with PBM mail order facilities. Recent data confirms that the generic dispensing rate of community pharmacies is at least 10 percentage points higher than the mail order generic dispensing rates of the three largest PBMs. However, as generic prices have increased in some cases due to shortages, PBM payments to community pharmacies have not kept pace.

Price fluctuations resulting from generic drug shortages prompt higher acquisition costs for these sparsely available products. If PBMs don't update their prices at the same time, generic dispensing is threatened. These unforeseen consequences of drug shortages can therefore have a huge impact on all involved in the drug distribution channel, especially on community pharmacies and our patients.

Conclusion

NCPA appreciates the opportunity to provide these comments as the Committee considers the complex issue of drug shortages. While drug shortages are multi-faceted and involve a number of factors, it is important to keep the safety of our patients as a top priority and work towards tackling the shortage factors that can be controlled and predictable. We remain committed to working collaboratively with Congress, the FDA, and relevant stakeholders in the supply chain to develop solutions that will minimize product disruptions and strive for prevention of drug shortages in the future.

AMERICAN SOCIETY OF HEMATOLOGY
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September 22, 2011

The Honorable Joe Pitts
Chairman
House Energy and Commerce Subcommittee on Health
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Frank Pallone
Ranking Member
House Energy and Commerce Subcommittee on Health
2415 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Pitts and Ranking Member Pallone:

On behalf of the American Society of Hematology (ASH), thank you for convening the Subcommittee on Health for a hearing on "Examining the Increase in Drug Shortages" on September 23, 2011. The Society appreciates the opportunity to share its concerns regarding the increasing problem of shortages of life-saving drugs. ASH's comments will describe how the problem of drug shortages is affecting hematologists and the patients we treat. In addition, these comments offer several recommendations for strategies to combat drug shortages. There is a critical need for changes in policies and practices to prevent patient harm and disruptions in patient care caused by shortages and ASH urges Congress to work with stakeholders, including the Society, to identify and implement effective strategies.

ASH represents over 16,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases, including blood cancers such as leukemia, lymphoma, and myeloma and a number of nonmalignant illnesses such as anemia (including sickle cell and thalassemia), thrombosis (including venous thrombosis, heart attack and stroke), and bleeding disorders. The patients our members treat have been especially adversely affected by recent shortages.

Although physicians have dealt with national drug shortages before, the increasing number of shortages of drugs in the United States has become critical and life threatening. Each year the total number of new shortages identified increases. Between 2006 and 2010, the number of new drug shortages tripled. What is even more alarming is that we continue to see increasing numbers of shortages this year, with close to 200 national drug shortages already reported as of August 31, 2011, compared to the overall total of 211 shortages reported in all of 2010.

The increasing number of drug shortages has significantly affected the practice of hematology because the standard therapies frequently used include older, sterile injectable products that are particularly vulnerable to production, marketing, and business factors. Fewer firms manufacture these products, the products require complex manufacturing processes, companies may be tempted to redirect resources to more

profitable products, and financial return may not justify corrective action when problems occur.

Over the past year, ASH has received frequent calls from hematologists, pharmacists and patients who experienced drug shortages and who requested help in finding supplies of the drugs or asked for guidance on alternative therapies. A spectrum of therapies has been involved, but the Society has heard the most concerns and questions about drugs used to treat multiple myeloma, lymphomas, and leukemias. In addition, a shortage of supportive care drugs has further complicated the lack of chemotherapy drugs.

The drug shortages already have had a profound impact on the care of some patients and, if not addressed, have the potential to place even more patients at risk. At a minimum, patients with serious hematologic diseases have been distressed if their treatments are delayed, even if this is for a very short time and not clinically significant. More significantly, physicians have had to choose initial therapies that are not their usual first-line of therapy standard treatment or have had to change therapies mid-treatment. Some institutions and practices have established policies to prioritize and ration the use of certain drugs during temporary periods of drug scarcity.

A widespread problem for hematology patients has been the shortage of cytarabine, part of standard therapy for certain leukemias and lymphoma. An ASH member recently shared his experience with the Society about a case involving a 50 year old male with primary refractory large B-cell lymphoma who was receiving chemotherapy to prepare him for a bone marrow transplant. The patient received the first part of the chemotherapy and was responding well. The treatment schedule called for cytarabine to be included in the second dose of chemotherapy, but because it was not available at the time, the physician was forced to choose an alternative therapy that was more toxic. The patient was not able to receive the transplant and died from complications.

This story is only one example of several cases that have recently been described to ASH about physicians having to give patients less effective or more toxic alternative treatments not because of a lack of coverage, prohibitively costly treatment, progression of disease, or lack of knowledge about how to treat, but, rather, because the standard treatment was not available.

The interruption in treatment caused by shortages puts vulnerable patients at risk. Physicians have been forced to send some of their most fragile patients to hospitals, pharmacies and clinics in geographically inconvenient locations to access remaining supplies of their therapy. Another ASH member reported several cases at his institution involving patients with pernicious anemia who were receiving monthly B12 shots. Because there was a shortage of the injections, the patients were faced with a multi-month interruption in their treatment, which exposed them to the risk of neurological damage and worsening anemia. The patients had the option to take oral B12 pills, but for most of them this was not a viable option because they were unable to absorb the alternate therapy through their digestive tract.

Practice management has also been affected. Practices typically hear about shortages when they order the therapy and find out that the supplier does not have the product in stock. Consequently, practices have had to spend significant time tracking drugs for patients who are scheduled for admission in the upcoming weeks. In addition, support staff and physicians are forced to constantly monitor multiple sources to track new and ongoing shortages. There has often been different information provided by the FDA, drug companies, and medical societies. Sorting through this information takes time away from direct patient care.

The cost implications of such shortages can be considerable. Traditionally, practitioners have been proactive in controlling health care costs by using generic drugs. However, because of shortages, practices have been forced to choose more expensive alternative treatments.

Drug shortages have also adversely affected clinical trials that are pivotal in research and treatment efforts. Trial activation has been suspended and patient accrual halted, ultimately slowing the pace of clinical research. For instance, a recently opened large **Eastern Cooperative Oncology Group (ECOG)** randomized clinical trial in Acute Myeloid Leukemia involving cytarabine and daunorubicin could not accrue patients and delayed the research.

ASH understands that the causes of drug shortages are multiple and complex. There is not a single solution. As different remedies are considered, there must be forethought to anticipate and prevent unintentional consequences of legislation or over-regulation. ASH recognizes that FDA cannot force a manufacturer to produce a product. Currently, FDA's ability to address drug shortages is compromised because of limited authority and resources. FDA cannot require manufacturers to notify it of all potential or pending shortages or impose penalties for not doing so; FDA has no authority to require companies to increase production of a drug during a shortage; FDA cannot impose an allocation plan when a shortage causes life threatening conditions; and FDA has limited ability to post timely information on its website for healthcare professionals and patients regarding reasons for shortages and timelines for resolution. Therefore, ASH believes it is critical that FDA have greater authority and resources and offers the following recommendations:

- **Increase FDA Authority** – ASH recognizes that the FDA currently does not have the authority to address many issues that cause drug shortages. *The Preserving Access to Life-Saving Medications Act* (S. 296/H.R. 2245) was recently introduced and proposes an expansion of FDA's authority.

  The legislation would give FDA the authority to require early notification from pharmaceutical companies when a factor arises that may result in a shortage. These factors may include changes made to raw material supplies, adjustments to manufacturer production capabilities and certain business decisions such as mergers, withdrawals or changes in output. The legislation would also direct the FDA to provide up-to-date public notification of any shortage situation and the actions the agency would take to address them. In addition, the legislation would require the FDA to develop evidence-based criteria for drugs vulnerable to a shortage; and would require FDA to collaborate with manufacturers of drugs vulnerable to a shortage to establish continuity of operations plans for medically necessary drugs. The legislation would also require FDA to develop an enforcement mechanism for non-compliance. This legislation would not fully solve the drug shortage problems we are experiencing, but it would be a significant step towards reducing the magnitude of the problem.

- **Improve FDA Communication with Stakeholders** – Information provided by the FDA, pharmaceutical companies, and medical societies about shortages frequently varies. The inconsistencies can be confusing to stakeholders and can complicate the management of patients. ASH recommends that the FDA increase its current communication with the pharmaceutical industry and medical societies to ensure that timely and accurate information is being delivered to all stakeholders. One basic way to improve and enhance communication would be to develop specialty-specific listserves. Any information that the FDA receives about a potential shortage could be filtered through the relevant listserve to all stakeholders. Also, if drug companies and medical societies are circulating information, they could share this information through the relevant listserve

as well. This should include information regarding specific drugs in shortage, length of time, and ways physicians may access therapies in short supply. This practice would ensure that all stakeholders receive accurate information in real time.

- **Examine Impact of Current FDA Requirements on Shortages** – Since approximately 42% of the 2010 drug shortages were caused by product quality issues, ASH recommends that the FDA examine how new testing methodologies involving more sensitive assays may contribute to the problem of shortages. While ensuring safety standards is paramount, FDA also needs to determine if its evaluation of product quality is accurate.

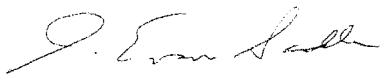
- **Develop a National Drug Registry** – ASH recommends that FDA develop a registry for older and medically-necessary drugs to better track quantities and availability of these drugs. A registry would facilitate FDA's ability to monitor potential shortages, share information with physicians and pharmacists, and assist providers in locating supplies of drugs in a more efficient way than through the current process.

- **Expand "Orphan Drug" Status to Incentivize the Continuous Production of Generics** – Many shortages have occurred because manufacturers are having a difficult time maintaining a profit margin under the current system. In an effort to encourage manufacturers to continue producing single source, older generic drugs, ASH recommends FDA consider classifying these therapies as "orphan drugs" and creating incentives for companies to manufacture these products.

The current drug shortage situation in the United States is unacceptable. The shortages have caused medical treatment to be delayed and compromised, research to be slowed or halted, and increased costs. Most significantly, shortages have caused patients to suffer. It is critical that FDA have expanded authority to mitigate drug shortages.

Thank you for your consideration of ASH's comments and recommendations. The Society looks forward to working with you on this urgent and most important issue. Please contact ASH Government Relations Manager, Stephanie Kaplan (*skaplan@hematology.org* or 202-776-0544), if we can provide additional information or expertise.

Sincerely yours,



J. Evan Sadler, MD, PhD
President, American Society of Hematology

cc: Members of the House Energy and Commerce Subcommittee on Health

GPhA
GENERIC PHARMACEUTICAL ASSOCIATION

TESTIMONY OF

THE GENERIC PHARMACEUTICAL ASSOCIATION

EXAMINING THE INCREASE IN DRUG SHORTAGES

BEFORE THE

ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

SEPTEMBER 23, 2011

The Generic Pharmaceutical Association (GPhA) represents the manufacturers and distributors of finished dose generic pharmaceuticals, manufacturers and distributors of bulk pharmaceutical chemicals and suppliers of other goods and services to the generic industry. Generic pharmaceuticals now fill 78 percent of all prescriptions dispensed in the U.S., but consume just 25 percent of the total drug spending.

According to an analysis by IMS Health, the world's leading data source for pharmaceutical sales, the use of FDA-approved generic drugs in place of their brand counterparts has saved U.S. consumers, patients and the health care system more than $931 billion over the past decade — $158 billion in 2010 alone — which equates to $3 billion in savings every week.

Introduction

We would like to begin by commending the Committee for your focus on this important issue. As members of the public who also are affected by shortages, the generic pharmaceutical industry is devoted to working with all stakeholders to minimize current shortages and mitigate factors that could contribute to future shortages. We are acutely aware of the distress caused to patients, families and clinicians by the shortage of medically necessary drugs. Drug shortages are a complex, multi-stakeholder issue and our industry is resolute in its commitment to be part of the solution.

Why are Shortages Occurring?

Before examining how best to respond to drug shortages it is important to understand why they are occurring. Contrary to some media reports, shortages are typically not caused by a manufacturer's decision to voluntarily discontinue supplying the product, and manufacturers do not — and would never — deliberately reduce the supply of essential medicines to push prices up.

Causal factors, rather, are numerous and do not apply in every case. They include everything from an insufficient supply of available raw materials to meet demand, to inadequate and delayed communications about shortages — both within the supply chain and also within and among the Food and Drug Administration's (FDA) enforcement and drug shortages personnel. Let us take a more in-depth look at these issues and how they can be addressed.

Insufficient Communication

As the regulatory authority charged with maintaining oversight of the U.S. drug supply, the FDA has stepped up its enforcement efforts to unprecedented levels in recent years. Due to the efforts of the FDA, the U.S. drug supply remains the safest in the world. GPhA applauds these efforts and is committed to working with the agency to ensure that patients continue to receive safe and effective generic medications. With the implementation of these expanded enforcement measures, however, comes a need for industry and the FDA to communicate at all stages of the process. Otherwise, these efforts may have the unintended consequence of adversely affecting our country's supply of critical drugs.

One way to do this is by implementing processes whereby remedial measures could be implemented without completely disrupting the manufacturing of necessary products. Through further remedial measures, the FDA could maintain its vigilance over the safety of the U.S. drug supply, while ensuring that patients are receiving the medication they need. It is also critical that the FDA and regulated industry increase early communication relating to all proposed or contemplated regulatory actions that would affect our country's supply of critical drugs.

Qualifying Alternative Suppliers

The pharmaceutical marketplace overseen by the FDA today is one that has become increasing global. Nearly 40 percent of all prescription drugs dispensed in the United States are now manufactured outside of the country, and nearly 80 percent of the ingredients in our drugs are manufactured abroad. According to FDA estimates, the number of drug products made outside of the U.S. doubled from 2001 to 2008.

Manufacturers face significant delays in the process to qualify alternate Active Pharmaceutical Ingredient (API) suppliers and secondary or redundant manufacturing facilities. As a result, many drugs have only one API supplier approved in their applications and are qualified in just one facility. This is in contrast to many other regions of the world, where supplemental API suppliers can be approved in as little as 30 days. Similarly, a prior approval supplement can take multiple years in the United

States while similar changes are accomplished in Europe and elsewhere in a much shorter time frame.

The FDA should bring its oversight in this area up to date with today's global pharmaceutical marketplace. A more streamlined and timely process for qualifying new or alternate raw material suppliers and alternate manufacturing facilities would allow manufacturers to increase production of medicines in short supply sooner.

And in the event an API supplier does cease production or is otherwise unable to provide adequate supply of raw material, the authority to approve new or alternate suppliers through a CBE-30 supplement would allow a manufacturer to more quickly respond to a shortage situation.

DEA Quotas

Currently, there are several controlled drugs on the shortage list. These products are strictly regulated by the Drug Enforcement Agency (DEA), and require a joint effort between the agency and generic manufacturers to assure that they do not fall into the hands of abusers.

In an effort to further help with these efforts, the DEA has put into place annual manufacturer-specific allocations of the materials used to manufacture controlled drugs. While GPhA supports the use of this quota system in order to ensure that these products are kept out of the hands of those who would seek to abuse them, in some

cases the system has left manufacturers with an inability to source sufficient API for controlled drugs. When combined with fluctuations in demand and shifting markets over the course of a year, the quota system has unintentionally contributed to the shortages of controlled drugs.

GPhA believes the DEA should be required to monitor the use of controlled drugs and adjust allocations accordingly for products in short supply. In addition, the FDA's Center for Drug Evaluation and Research (CDER) and the U.S. Attorney General should establish a process to streamline manufacturing production quotas in response to drug shortages. If one manufacturer ceases production, the Attorney General should have the authority to quickly increase the quota of another manufacturer.

Collaboration Among Stakeholders is Needed

Despite all of these factors currently contributing to shortages, there are still numerous opportunities for generic manufacturers, and all stakeholders, to work together in an effort to solve the problem.

For example, there is a need for the agency to implement a formal communication process by which manufacturers can communicate real and potential shortages. The FDA's drug shortage staff currently plays only an informal role in this area, serving as a conduit to communicate the supply status of critical shortage drugs among manufacturers and other branches of the FDA. A formal communication process that

includes not only manufacturers, but also wholesalers, specialty distributors and group purchasing organizations is needed.

Further, GPhA encourages the FDA to work with manufacturers to develop guidance that better outlines the process for suppliers to proactively report drug shortages to the agency's drug shortage staff, and to develop a defined and updatable list of all medically necessary drugs. Manufacturers are currently working with the FDA to prioritize the supply, and maximize the capacity and redundancies of these products.

Finally, GPhA believes it is critical that all manufacturers, in partnership with the FDA, develop successful strategies to assure the highest quality products, while concurrently aggressively addressing any issues that may lead to drug shortages.

Conclusion

In conclusion, Chairman, GPhA is committed to working with the FDA and all stakeholders to minimize current drug shortages and prevent future shortages from occurring. Nothing is more important to our industry than ensuring patients have access to their lifesaving generic medications, and with a joint effort among all involved we believe we can make a significant step toward accomplishing this goal.

Mr. PITTS. I recognize this time the gentleman from Illinois, Mr. Shimkus, for 5 minutes.

Mr. SHIMKUS. Thank you, Mr. Chairman.

I think all would agree that resources matter in this tough fiscal period, as the ranking member said. I think also part of our issue would be prioritization, especially in life-saving issues and what are agencies doing to put first things first and what can they do obviously redirect funds in a different direction.

For Dr. Koh, going in line with my opening statement, how have cost and payment factors impacted these drug shortages?

Mr. KOH. Well, again, this is an industry that is producing products in an environment where they are facing increasing economic pressures. The profit margin for any particular agent is declining for them, so they have to make business decisions but also keep their products moving until the decision is made, perhaps to discontinue a product. On the quality manufacturing issues and possibly delay issues and what is often a complicated production process, it just all contributes to the situation that we are seeing now.

Mr. SHIMKUS. And who are the big payers?

Mr. KOH. Well, there is a process where purchasers—hospitals and physicians and providers—buy these products but there are also group-purchasing organizations and pharmacy benefit managers who are trying to drive down the price for understandable business reasons. So these are all the stakeholders who are involved in the purchasing chain.

Mr. SHIMKUS. And I do appreciate your opening testimony because we had a series of questions and really you answered them in your opening statement. And I am just going to highlight one of the things was a question we were going to ask was closely collaborating and you gave the example of the drug with the crystallization, and I thought that was very helpful.

The other issue I was going to focus on was alternative sponsors, and that is where you talked about maybe temporary easing import restrictions or importation or—I can't even read my writing—temporarily doing something else. But you said that is constrained based upon if there is a shortage overseas of the same product, and something that we have talked about over the past years with Ranking Member Dingell is the ability to make sure that the drugs that we are importing are inspected by our inspectors so we know the efficacy and safety of that.

I have always been a risk-based person on the focus point of saying that those that are more questionable facilities ought to get a lot of look. If they have been operating safely and they have inspected like a U.S. facility every year, then it might make that you could go every 2 years or maybe every 18 months. And that is the whole issue of shifting sources, too, to the more critical elements and safety versus known products and industries that you all have real confidence in. We want to expect you to do that in industries that have a poor record, but those that you have really good confidence in, that is the funding issue.

You also mentioned, you know, business reasons and aging facilities and I think you mentioned increased regulations. Is that part of your testimony?

Mr. KOH. Well, the quality standards that the FDA puts forward in areas like this have been unchanged for the last 4 decades. And in fact the FDA has really gone the extra mile in my view to show tremendous regulatory flexibility here. So again, since we can't require any manufacturer to do much of anything, all we can ask is for information, communication, collaboration, and then the FDA shows maximum regulatory flexibility. This re-warming of the cytarabine that I mentioned to you is one example of filtering out particular matter so again these medications can be used and not put aside is another example.

Mr. SHIMKUS. Yes, I only have 12 seconds——

Mr. KOH. Sure.

Mr. SHIMKUS [continuing]. I will go back to the testimony——

Mr. KOH. Um-hum.

Mr. SHIMKUS [continuing]. Because I did scribble a note a comment on increased regs, and I will have to go back and look at that. But why doesn't the shortage of a product in this sector then send an increased price signal to manufacturers for them to then produce the good?

Mr. KOH. Well, we have come to learn that the standard economic principles of supply and demand——

Mr. SHIMKUS. And the question is why is that distorted? I think that is the basic fundamental question of this problem. What has distorted the fundamental principle of supply and demand, and my time has expired, but I think that is the heart of this issue. I yield back my time.

Mr. KOH. Sure. And I am sure Dr. Kweder can add, too. First of all, these agreements are made often through these long-term contracts and so also this whole process involves multiple stakeholders, especially and including the pharmacy benefit managers and the group purchasing organizations. So it complicates this environment and sort of does not make relevant the sort of standard supply and demand economic principles that we see in other businesses.

Mr. PITTS. Dr. Kweder?

Ms. KWEDER. You have said what I would say. Thank you.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentlelady from Illinois, Ms. Schakowsky, for 5 minutes for questions.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman.

I, too, am sponsor of the DeGette legislation that would ask for early notification. I just wanted to mention we actually have a Chicago-based injectable drug company Hospira that has endorsed the bill and they already do many of the things including proactively reporting to the FDA about potential drug shortages.

You have explained, Dr. Koh and Dr. Kweder, the advantage of that early notification. Let me just raise a question that some have raised. Early warning could exacerbate the problem and lead to hoarding of critical drugs. Is this anything we need to watch out for, account for? I mean I am hoping that that is not the result of this legislation, obviously, which I support. Have you heard of that?

Ms. KWEDER. I will respond to that question. When we are notified of a potential shortage, we do not automatically turn around and put that on our Web site and notify the public of a potential

shortage, which would have the opposite effect of what we want. We judge very carefully when is the right time to make a public announcement about a potential shortage. First, we assess what are we talking about? Is this a true product shortage or is it an imbalance in distribution? Because sometimes you see things that seem to be in shortage in one part of the country but there is plenty of it and more so in another part.

So we take that potential for making things worse very, very seriously. We meanwhile are working on it to assess it and assess what we might do to mitigate it if it is real. If it is real, we usually announce the fact that it exists and try to let the public know what we are doing to try to address it.

Ms. SCHAKOWSKY. So early notification, then, is something that is a very useful tool?

Ms. KWEDER. Right, early notification to FDA is a very useful tool. We see that as different than early publication.

Ms. SCHAKOWSKY. Got it. Let me ask you this. The FDA has limited authorities. Let me run through some of those. At this point you can't require manufacturers to do this early notification, you have no authority to require companies to increase production of a drug during a shortage, you can't impose an allocation plan when a shortage causes life-threatening conditions, and FDA has limited ability to post timely information on its Web site for healthcare professionals and patients regarding reasons for shortages and timelines for resolution. I don't really understand that one. But in addition to early notification, are there other authorities that you need that would help mitigate this problem?

Ms. KWEDER. I think there are 2 things. One, in the early notification is something that helps us in the mitigation and prevention greatly. What we need to be able to do is we need to be able to have the industry assure that they are making a quality product and upholding their responsibility to produce high-quality products where these things won't happen. Our goal is to prevent even the potential for a shortage from occurring, not always possible.

In the case of many of these threatened and real shortages, as Dr. Koh said, these are in plants that manufacture multiple, multiple products. If you look at the record, the things that led to the actual problem with production are things that we have been telling the companies about in routine inspections for years but only became critical in order that they needed to address these, modernize, so that they could continue producing quality product without a glitch.

So that is first and foremost from our standpoint, assuring that we are aware so that we can step in and use every possible communication tool and flexibility and regulatory action.

Ms. SCHAKOWSKY. Let me just ask you to what extent is the issue of business decisions—what percent of those cases where we have shortages would you say this is a business decision?

Ms. KWEDER. You know, I can't give you an exact percentage. I will be happy to provide that follow up.

Ms. SCHAKOWSKY. Is it a major issue and is there anything that we can do about that?

Ms. KWEDER. I would say that it is not. That is not the major issue.

Ms. SCHAKOWSKY. OK.

Ms. KWEDER. I would say by far and away the more common scenario has something to do with manufacturing and product quality.

Ms. SCHAKOWSKY. Thanks you. Thanks to both of you for being here.

Mr. KOH. Thank you.

Mr. PITTS. The chair thanks the gentlelady and recognizes the gentlemen from Kentucky for 5 minutes for questioning.

Mr. GUTHRIE. Thank you for being here. I am just going to follow up a little bit on Congressman Shimkus. I mean you answered a lot of the questions in your opening testimony. But I had a group of oncologists in the other day. These aren't people that make drugs, they aren't people that sell drugs, people that—FDA issues or whatever you want to—these are guys just are taking care of patients, and they say they literally have to make choices about who they take care of because they don't have the drugs available. So I ask kind of the questions, say, well, I can't believe a company won't make them if you have the demand for them. And they told me that this particular type of drugs, the generic are priced different in the Federal Government. So the Medicare actually prices these different than other drugs. Was that what they were saying was true?

Mr. KOH. Well, I can start with that. And first of all, Congressman, thank you again for your attention to the patient. This is a dire situation for patients and I have actually trained in cancer as well as other fields so this is very personally and professionally important to me.

We have a rule of Medicare here that reimburses according what is called the average sales price, so that is one factor here, but we don't view that as a significant issue in driving the shortages that we are seeing here.

Mr. GUTHRIE. But these generics are a different system than others because what we are seeing is you mentioned that pharmacy benefit managers, all these are driving down drug costs where they are doing it, you know, a pharmacy benefit manager is trying to do all drug costs.

Mr. KOH. Sure.

Mr. GUTHRIE. But we seem to see this particular class of drugs having a bigger problem than others and the only thing that I can see that is different is the way the Federal Government treats them. They treat them different than other drugs.

Ms. KWEDER. I am not sure I can answer your question but these are generic drugs. They are off patent for the most part. You know, there are some that—so they are at a point in time where the profit margin for the drugs—generally because they are generic and you can have multiple manufacturers—is lower.

Mr. GUTHRIE. Right.

Ms. KWEDER. And it wouldn't be just—you mentioned Medicare, CMS, but there are many other group purchasers—some of them are government-related, others are private insurance companies that are negotiating in bulk basically of prices. And they are no different than what the Federal Government does. It is the same.

Mr. GUTHRIE. But why isn't that happening in other classes—I mean this seems to be particularly more than others.

Ms. KWEDER. Well, in the other classes, in the non-generic world, there is one source.

Mr. GUTHRIE. Um-hum.

Ms. KWEDER. And so they are in a great bargaining position because they are a sole source, the innovator product, they have a patent.

Mr. GUTHRIE. But there is a different system for generic drugs in Medicare than——

Ms. KWEDER. They tend to be priced lower.

Mr. GUTHRIE. Priced lower?

Ms. KWEDER. Absolutely. And that, of course, is the access point for the public.

Mr. GUTHRIE. Right, if you have lower costs, which we all want to drive lower costs, believe me. We are all trying to save—but you have lower cost, then you get less supply as you are saying because the prices are obviously lower and you have less quality of people producing. And so according to the oncologists there is not a mechanism where if just you pay just a little bit more, you are going to get the drug that is going to take care of—you know, there is not a price mechanism to say we have got a low supply that Congressman Shimkus is talking about. Therefore, if we can adjust the price, we get the supply that we need to take care of patients.

Mr. KOH. Well, the situation is summarized by Dr. Kweder, but Congressman, I think you were raising some interesting points where we can get you more information——

Mr. GUTHRIE. OK.

Mr. KOH [continuing]. And work with you.

Mr. GUTHRIE. Because whatever we can do—I mean the things that you mentioned, business decisions, that is all part of the mix but there are some things we can do from this side.

Mr. KOH. Thank you.

Mr. GUTHRIE. And one other thing just quickly on the FDA, the 2 to 3 years you said, now you have got the flexible teams, is that relatively new? Because after these oncologists said this I reached out to some people and they did talk about some issues with inspection and inspection time like Congressman Shimkus. So it is being addressed——

Ms. KWEDER. Absolutely, it is being addressed. It absolutely is being addressed.

Mr. GUTHRIE. OK. Maybe just hear from the ones who have the worst experiences I guess but that is good because I know with your physicians and the oncologists I met, you take care of patients, so I appreciate your attitude in moving forward to do so.

So thank you and I yield back.

Mr. PITTS. The chair thanks the gentleman and now recognizes the ranking member emeritus of the full committee, the gentleman from Michigan, Mr. Dingell, for 5 minutes for questions.

Mr. DINGELL. Mr. Chairman, thank you for your courtesy and thank you for holding this hearing.

Let me begin by asking this question yes or no. Do you have authority at FDA or at HHS to waive any of the requirements with regard to efficacy, good manufacturing practices, or safety, yes or no, in the event of shortage?

Ms. KWEDER. Yes.

Mr. DINGELL. You do have it?

Ms. KWEDER. We have the authority to use flexibility in how we implement the regulations.

Mr. DINGELL. OK.

Ms. KWEDER. Regulatory discretion.

Mr. DINGELL. I would like to have a further answer on that particular point.

Ms. KWEDER. But the requirements are the same. How one reaches them is flexible.

Mr. DINGELL. OK. I would like to have further statement on that for the record so we can understand what your authority there is.

It is my understanding that the FDA has been working to address shortages of medically necessary drugs. Can you please define what medically necessary means, please?

Mr. KOH. Medically necessary is defined as a product used to treat or prevent a serious disease or condition for which there is no other product available to act as a substitute.

Mr. DINGELL. I believe you have indicated in your testimony that the vast majority of shortages experienced in the United States is attributable to sterile injectables. Is that correct?

Mr. KOH. Yes, sir, that is correct.

Mr. DINGELL. And according to your testimony, the majority, some 54 percent of these shortages were due to "product quality issues such as particulates, microbial contamination, impurities, stability changes resulting in crystallization." Is that right?

Mr. KOH. That is right, Congressman.

Mr. DINGELL. Were you finding those in American pharmaceuticals or imports?

Mr. KOH. We were finding them here in the United States.

Mr. DINGELL. What about imports?

Mr. KOH. Well, those are exactly issues we try to prevent which is why importing is always a challenging issue. In fact——

Mr. DINGELL. Yes, but you have really no authority to address the question of the manufacturing practices abroad. You have no real authority to deal with good manufacturing practices. You have no real authority to see to it that the requirements that are imposed on American manufacturers for safety, efficacy are there, and you have very little power to effectively inspect those foreign manufacturers either of finished pharmaceutical products or components and constituents, right?

Mr. KOH. That is correct, Congressman.

Mr. DINGELL. And you have no ability, really, to know who is manufacturing these things or to trace them through the product line, is that right?

Mr. KOH. That is right. That is why the importation process is done very carefully and selectively.

Mr. DINGELL. I have got some legislation to address that and I hope that we will be shortly addressing it here in this committee.

I have a bill, as I mentioned, where we address the problem of quality problems in drug manufacturing process by requiring the drug manufacturers implementing effective quality system that complies with GMP. The quality system would also be required to ensure risk management procedures that would address all relevant factors through the supply chain, including original source

materials and their origin, onsite audits, and methods to detect or include potentially risky substances. Manufacturers would also have to maintain records and establish that the drug was manufactured and distributed under conditions that ensured its identity, strength, quality, and purity. Would legislation of this kind help you address quality issues?

Mr. KOH. Yes, tracking quality every step of the way would certainly uphold patient safety.

Mr. DINGELL. This is a matter on which I have worked with the gentleman, my colleague Mr. Shimkus. Now, it has been widely reported that when information becomes public about a drug shortage, an active gray market tries to sell drugs in short supplies to pharmacists or hospitals. Does this present a safety concern?

Mr. KOH. Yes, it does, Congressman.

Mr. DINGELL. Why and how and what can you do about it?

Mr. KOH. Well, this is largely unregulated. The Federal Trade Commission is involved to some degree but unfortunately——

Mr. DINGELL. They don't have the expertise that you have and would you submit to us a proper answer informing me what we have to do to address that particular problem?

Mr. KOH. I would be happy to do that, um-hum.

Mr. DINGELL. Now, when drugs are purchased in the gray market, do we know if these drugs have been stored properly to ensure effectiveness, whether the drugs have been diluted, or whether the drugs are free of filth contaminants or adulterates? Yes or no?

Mr. KOH. No. Unfortunately, we know very little about the products in the gray market.

Mr. DINGELL. Now, as I mentioned, I have a bill that would require manufacturers to maintain records establishing where the drug and its raw materials were produced, including all information relative to producers, manufacturers, distributors, and importers. Would such legislation and such power assist Food and Drug in assuring the safety of these kinds of pharmaceuticals? Yes or no?

Mr. KOH. Yes, we want to uphold the safety and quality, so thank you for that.

Mr. DINGELL. At the end of the day, American consumers and patients are facing 3 problems: 1) the drugs, they need to be available and affordable; 2) are there drugs they need safe; and 3) are they efficacious? Do they work?

I believe the committee needs to examine these issues carefully and swiftly. Our colleagues in the Senate, Mr. Harkin and Mr. Enzi have already called on Food and Drug to improve its oversight of the pharmaceutical supply chain. I would hope this committee would follow suit, but I would like to have you give us a statement of what authorities you need to adequately carry that out. I don't believe that sending you a letter asking you to do something for which you have no authority works. Would you submit, please, for the record because my time is up what it is that has to be done to give you the authority to address those problems?

Mr. KOH. I would be happy to, Congressman. Thank you.

Mr. DINGELL. Thank you. Mr. Chairman, I thank you for your courtesy. I ask unanimous consent that the responses be inserted in the record upon receipt?

Mr. PITTS. Without objection, so ordered.

Mr. DINGELL. Thank you.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from Louisiana, Dr. Cassidy, for 5 minutes for questions.

Mr. CASSIDY. Hello. Thank you.

Now, you do have the ability to import from overseas obviously, and there were issues raised regarding adequacy of quality control if you will. We think of Hepburn from China causing many deaths, correct? One of the issues that was raised here in a previous hearing was that the inspectors, as part of their union contract, can refuse to go overseas. And so I think Mr. Pallone spoke about inadequate resources, but the issue was that here there was enough money to inspect or a requirement to inspect a pharmaceutical every 2 years and there is happening only every 9, and when I ask could we just redirect resources to send that person over to maybe alleviate some of these by expanding importation, the point was that the unions would not allow this to occur. They had the right to refuse the overseas assignment. Is that true and to what extent is that limiting our ability to approve the APIs—I forget the acronym but you know what I am speaking of.

Ms. KWEDER. In the terms of a shortage situation, that has not been a big issue. For the most part, when we have a circumstance where some inspection activity is necessary in order to prevent a drug shortage, we find that our staff are extremely cooperative and willing to roll up their sleeves and step in. We are addressing the issue of our inspection force more broadly in parallel to this, but it has not been a critical issue in mitigating or preventing drug shortages.

Mr. CASSIDY. But there are a heck of a lot of generics being manufactured in India and other Third World countries so are they just not producing the ones that we are in short supply of or are we just not confident of the quality of the product which they produce?

Ms. KWEDER. I am not sure I understand your question.

Mr. CASSIDY. So is there a worldwide supply of drugs that are currently in shortage here? It is just that we are not trusting the manufacturing process by which they are produced and therefore do not allow their importation?

Ms. KWEDER. I would say the lack of allowance to import a product has been unusual. If there is a foreign source, we are usually able to work through and get it approved. There have certainly been circumstances where there have been important problems that would prevent that, but in most cases if there is a foreign source and going to a foreign source is necessary, we are able to work through that.

Mr. CASSIDY. OK. In the gentleman who is going to testify from Teva, he speaks about how DEA has a quota for controlled products and that if somebody goes out of business, that quota might not necessarily be assigned to another manufacturer, and so you have a kind of centrally planned economy-induced shortage. Any comment on that and any way we can address that?

Mr. KOH. I can start. I know that controlled substances represent only a very small part of the drug shortage situation that we are talking about, so we do work with DEA but it is limited only to several instances. And Dr. Kweder might add more.

Ms. KWEDER. And it is more complicated having the DEA involved for obviously good reasons. It does create an additional step and complicates this, but we work closely with the DEA when a controlled substance shortage is at issue.

Mr. CASSIDY. And I understand that but is there any plans to make it so that if somebody stops producing their quota it is transferred to someone who would? Because I gather that is not the situation now. And although we are working closely, that is an obvious solution that I am not sure is being implemented from your statement.

Ms. KWEDER. We are continuing to try and figure out how to expedite these kinds of issues with DEA. And I don't have an answer for you about exactly when that will be resolved, but we are committed to doing it, as are they.

Mr. CASSIDY. OK. Teva also mentioned—just because I, you know, I like to read what the other panels say so I refer to this—that the "speaking of a source or an active pharmaceutical ingredient," they say that the qualification process to identify a supplier for such can be very onerous, the qualifying gain after you get approval for a new API supplier or alternative manufacturing site for an already-approved supplier can take as long as 2 to 3 years. Now, I am channeling my inner Teva wherever Teva is. You don't have to testify anymore, but what would be your response to that?

Mr. KOH. Again, these are areas where we are trying to show as much regulatory flexibility as possible to accelerate approvals when necessary. So we often address these themes through the maximum flexibility possible.

Ms. KWEDER. And we already do. Whenever there is an issue related to a supplier where it requires FDA to approve a new supplier or even a new facility, I think that was one of the other concerns. We turn those around very, very quickly.

Mr. CASSIDY. What would——

Ms. KWEDER. In a matter of weeks to months. These are not business as usual where there is a long wait time. We understand that patients are at the end of this line and we need to do everything possible to get on the case and work with the companies. And we have done that with Teva.

Mr. CASSIDY. OK. I yield back. Thank you.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from Utah, Mr. Matheson, for 5 minutes for questions.

Mr. MATHESON. Thank you, Mr. Chairman. I appreciate your yielding time to me and I appreciate you holding this hearing. I think we have established the problem. I am sure lots of people have talked about circumstances in their district. I represent the University of Utah. They project more than 360 products having shortages and that many products by the end of this year. And I was at the Huntsman Cancer Institute just 2 weeks ago and they were talking to me about the challenges they are facing. So I guess everybody up here has a story, but I thought I would tell you it is in my backyard as well.

I was wondering if you could address for me some of the concerns about gray market activity as a result of these drug shortages and the integrity of what is out there, the quality of the medications

if they are counterfeit or how we can address some of these challenges of a gray market when these medications have shortages.

Mr. KOH. Well, I can start. And first of all, thank you, Congressman, for your commitment to research. We didn't say explicitly but we can say now that this drug shortage issue is dramatically affecting clinical trials as well in cancer and infectious disease in many parts of NIH, so that is very, very troubling to us as a Nation that prizes scientific advances.

The gray market, unfortunately, is very poorly understood and, as we have mentioned already, it is largely unregulated. And to have now this dimension complicating an already complicated situation is very disturbing. So we appreciate your attention to that and we want to address that as well as all the other factors that are involved here.

Mr. MATHESON. Are there actions we should be taking on addressing the gray market specifically or should we really just be addressing on the underlying problem of the shortage of these medications? Is that the more valuable way to address—that would eliminate the gray market problem I guess if we don't have shortages?

Ms. KWEDER. One of the questions that was asked previously was about what we know about the products that appear on this gray market.

Mr. MATHESON. Right.

Ms. KWEDER. Do we understand when they expired, where they came from, and are they made by the company that is experiencing the shortage or are they counterfeit products? We don't because we don't have a tracking system within the drug supply to know what product comes from where.

Mr. MATHESON. I appreciate that. I will do my 30-second advertisement. I just introduced with Mr. Bilbray this week our track and trace legislation, pedigree legislation for maintaining the integrity of the drug supply in this country. We are operating on rules that were created in 1988 and the world has changed. I don't think this is going to be on the topic of this hearing, but there is just too much money on the table for the counterfeiters in terms of the U.S. pharmaceutical marketplace, and I hope this committee can take a look at this legislation Mr. Bilbray and I have introduced because I do think it is an important safety factor for the integrity of our supply in general.

I appreciate your coming here for this hearing. Mr. Chairman, I yield back.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentlelady from Tennessee, Mrs. Blackburn, for 5 minutes for questions.

Mrs. BLACKBURN. I want to thank our witnesses for being here, and as you know, some of us arrived a little bit late. We did have the Solyndra oversight hearing going on downstairs, so we completed that one before coming up. But we are grateful that you are here and our second panel of witnesses we are also looking forward to. And I am glad we have a Tennessean on that panel who will be joining us.

Just a couple of questions. As you can see, we are going to look at how we address this issue and having you here helps to inform

our decision-making process. So a couple of things I would like know, and if you don't have the answer for me, please submit it to us so that we can include it in our record.

I wanted to see if each of you had any examples where you had worked closely and collaboratively with your agencies with manufacturers' drugs where there was a known or a projected shortage and see if you could articulate what that process was, the interface that transpired there. And if you have those examples, ma'am, please go ahead and give them, and if not, we will accept those in writing.

Mr. KOH. So Congresswoman, I can repeat the example that we are very proud to share actually here for the first time that had to do with cytarabine, which is a——

Mrs. BLACKBURN. OK.

Mr. KOH [continuing]. Lifesaving drug used for acute leukemia. And this shortage received tremendous national publicity and represented a dire challenge for cancer patients. And so when the FDA worked with the industry on this particular drug, they found that one of the issues complicating the production was the crystallization of the drug in the solution and that re-warming it would restore the safety features that would allow infusion into patients. So with that collaboration between the FDA and industry, that issue has now been recently resolved and we are very, very pleased to report that. And I know my colleague has other examples.

Ms. KWEDER. I actually would like to expand on that one——

Mr. KOH. OK.

Ms. KWEDER [continuing]. Because before the issue of the crystals in the vials, where the cytarabine shortage began was it was being made by 3 companies but the majority of the supply was being made by one firm. They were experiencing significant production delays, so what FDA did was we contacted the other manufacturers to work with them to increase their production in order to be able to supply the market. In the course of them increasing their production and trying to produce product rapidly, the crystallization occurred in both facilities. So that preceded the crystals. We then resolved that activity as well. So in that case, we also, when there was concern about whether we would find a solution to the crystallization, we also investigated alternative manufacturers, whether there were any overseas. We were not able to identify any alternative manufacturers. They were all U.S. firms.

Mrs. BLACKBURN. Let me interject there. Do you have examples other than this one? Are there examples where you worked with some of those alternative manufacturers and brought them into the fold, and then once you identify that there is a near-shortage that is approaching, do you think that there is a way through the production process or the compensation model to provide incentives so that you have a more predictable supply?

Mr. KOH. Well, another example that we can provide for you, Congresswoman, has to do with purple fall, which is an agent that is used in anesthesia. And when those shortages started occurred, the FDA could facilitate temporary importation of a substitute agent to help ameliorate that situation. So that is yet another example and I know the FDA has many others. The economic issues here are so complex that offering any economic solution requires

first a careful analysis. And we are trying to do more of that, especially through our assistant secretary for planning an evaluation and we hope we can come out with some more definitive recommendations for you in that area in the near future.

Mrs. BLACKBURN. Thank you. We appreciate that, and in the interest of time, I will yield back.

Mr. PITTS. The chair thanks the gentlelady and recognizes the gentlelady, Mrs. Myrick, for 5 minutes for questions.

Mrs. MYRICK. Thank you, Mr. Chairman. And thank you all, all of our witnesses for being here. I was also at another hearing so I am sorry I missed your testimony and some of the questions.

Like everybody else, our area is experiencing the same problems and our doctors, we meet with them constantly. But particularly in anesthesiology and oncology as you well know, we have the problems. And it is scary from the standpoint of what could happen with somebody if they are given another drug that really doesn't either work or they, you know, have a reaction to it or something. And thank you very much for any efforts in trying to get to the bottom of it.

And I wanted to ask if really the consolidation has taken place in the drug industry over the last few years and continues to place, you know, what effect or how does that contribute to the problem that we are seeing today? I mean is this a large contributing factor because of fewer manufacturers available?

Mr. KOH. Thank you, Congresswoman, for your interest and support. And yes, we view industry consolidation as one of the driving causes here, and as you can imagine if you are a denominator of or a manufacturer shrinks and then any one of them has a manufacturing problem or delay, it really puts the onus on the others, and if the others don't happen to produce that product and if this particular company is a sole source producer, then you have the number of occasions that we are seeing right now. So there is no doubt that industry consolidation has contributed to this.

Mrs. MYRICK. So what if any recommendations do you have of how we get over this hump? Because, you know, you mentioned the generics which we are all very much aware of and the fact that are just as popular to do because of the cost factors and other things that have entered into it. I mean what is it that you think we should be doing or looking at to try and get to the bottom of how we can help with this.

Mr. KOH. Well, we again want to stress the importance of communication and early notification because that will help all parties to work together. And as the number of industries involve shrinks, we want to really maximize our communication with those manufacturers, and we are doing so as we speak. And then as Dr. Kweder mentioned, we also want to have more assurances that the products that are being produced have high quality so that we don't run into these quality and manufacturing issues. So those are 2 things that would be very helpful to us.

Mrs. MYRICK. And you find the companies work well with you?

Mr. KOH. We have had excellent dialogue to date and I want to do much more of that, not just the FDA but the entire department and also engage the public in this as you have heard.

Mrs. MYRICK. Thank you. I will yield back, Mr. Chairman.

Mr. PITTS. The chair thanks the gentlelady and recognizes the gentleman from Pennsylvania, Dr. Murphy, for 5 minutes for questions.

Mr. MURPHY. Thank you. And I thank this distinguished panel and we appreciate your concern for our citizens of this country.

A couple areas here. Are you meeting with the manufacturers? I want to ask a couple questions to find out here with regard to what are some of the causes of this drug shortage. You laid out a number of these things very well, thank you. But let us say, for example, cancer drugs. Why the shortages with cancer drugs? We know they are very expensive in many cases. What specifically is the reason for that?

Mr. KOH. Well, it is very distressing, Congressman, some of these time-honored lifesaving medications now being caught in the middle of this public health crisis and some of the agents we have mentioned here, cytarabine, vincristine, bleomycin, time-honored agents that have been shown to be effective for decades are now stuck in these shortages. So again these are older generic sterile injectable drugs that are typical of the ones that are being——

Mr. MURPHY. But can I ask specific things. Do we not have enough manufacturers, for example, working on these things? Is that part of the problem?

Mr. KOH. That is part of the problem, again, because the industry has consolidated and so we don't have the dozens and dozens——

Mr. MURPHY. Of those who are there, are they not working at capacity? Do we know if that is an issue?

Mr. KOH. I am not sure I can address that directly.

Ms. KWEDER. I think that what often happens in a lot of these companies, they make dozens of products.

Mr. MURPHY. Um-hum.

Ms. KWEDER. These sterile injectables can only be made in certain types of facilities so there are a limited number of those. And because of the market and the few number of producers, there is pressure to produce and continually produce. And so maintenance of the facilities themselves is often put off because it requires an investment on these low profit margin——

Mr. MURPHY. They are expensive, the low profit margins?

Ms. KWEDER. Right. Some of them are not terribly expensive but low profit margin. So there is——

Mr. MURPHY. That is important what you just said. So this is one of the concerns we have. Certainly, we want medications to be affordable. I mean why window shop when you can't afford, but in our push to make sure that drugs are affordable, are we also tripping over ourselves? It is hurting the patients when we say we want there to be such a low profit margin that it ends up backfiring and we don't end up with the medications that save lives? Is that part of our policy that is getting away for us?

Mr. KOH. Well, thank you for posing those questions and obviously ultimately our goal is to protect the patient and give timely delivery of a lifesaving medication——

Mr. MURPHY. And even if you don't have the information today, is that something you could advise us on? I am looking for anything politics aside. I really want to know from the standpoint of

myself as a healthcare provider. If we are doing something that is saying we want drugs to be affordable but we are cutting the price so much that people don't want to make them, that is a serious concern. And so my question is policy interference. If you can't answer that today, I just want to know if you will get back to us with that.

Mr. KOH. Sure, Congressman. Those are precisely the issues that we are wrestling with as a department and as a country. So thank you for posing that.

Mr. MURPHY. And I say this from the standpoint of, look, what oftentimes what goes around the Hill is lots of accusations and politics. We can't afford to engage in any of that on these lifesaving issues. And so I am trusting you to give us those honest answers and I really appreciate it from one colleague to another here.

Mr. KOH. Thank you so much, Congressman.

Mr. MURPHY. And also with regard to inventories, I am hearing that hospitals are saying they are having a hard time keeping their inventory. It is not an issue that they are not purchasing enough, correct? Or is it? If a hospital says we can't have some of these things in supply because it may be too expensive or too difficult for us to keep these in inventory because of special requirements for how to maintain them, how to secure them, the special conditions under which they might be—is that part of the problem, too, they may not be ordering enough because for themselves it is also very expensive?

Ms. KWEDER. I believe that it can be a problem. There also has been a trend—this is certainly not 100 percent but there has been a trend in the industry to have what some people call just-in-time production.

Mr. MURPHY. Um-hum.

Ms. KWEDER. They don't have the long lead time at production that may be—particularly for these sterile injectables that there may be for other products that have longer shelf lives. So they tend to make less and distribute it out in smaller amounts——

Mr. MURPHY. Um-hum.

Ms. KWEDER [continuing]. Which certainly contributes to hospitals not being able to maintain a large supply and cushion in addition to what the other concerns that you mentioned——

Mr. MURPHY. And again, the just-in-time inventory is one where they are thinking that they also have a small margin. I mean it is one of these things, look, we understand healthcare is expensive. Sickness is more expensive and we all want to work together. And so I do appreciate and look forward to seeing your information on this. Thank you very much.

I yield back, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman from Georgia, Dr. Gingrey, for 5 minutes for questions.

Mr. GINGREY. Mr. Chairman, thank you very much. I am sorry I missed a lot of your testimony, witnesses, but thank you for being here.

Let me first address to Secretary Koh, in your testimony you cite that there were 178 drug shortages in 2010 and that sterile injectable drugs make up a large and increasing share of these shortages and by my count, roughly 132 of the 178 were for sterile

injectables. Of these injectable drugs, can you tell me how many were in shortage in previous years? Has it been a long-term problem or just more recently?

Mr. KOH. This is a long-term problem, Congressman, and unfortunately, the trend is going the wrong way. The shortages are increasing year by year. We did it back through 2006 and the trend is getting worse since then.

Mr. GINGREY. And then tell me this. Are there any other common characteristics that you are aware of among these 132 besides the fact that they are generic and they are sterile injectables? For instance, are these drugs typically newer generics or drugs that have been on the market for years? Actually, you just answered that and I thank you. Well, the other thing on that is are the profit margins typically very low or any other issues that you might be aware of?

Mr. KOH. So on the first question, Congressman, the irony here is that these are older generic drugs that we understand are very helpful if not lifesaving and so to have this situation is really quite ironic and tragic. And you are right, there is an issue with respect to business forces here and the profit margin is understood to be quite low for many of these individual products.

Mr. GINGREY. And my last question can really go to either one of you, Mr. Secretary or Dr. Kweder. Am I saying that correctly? Good. Help me understand something. Mr. Shimkus earlier addressed this. Many of the drugs we are talking about are these older generics, not just the sterile injectables, where the profit margins can often be very low. These low profit margins can oftentimes lead to very little competition or even drugs for which only one company make the product. Mr. Shimkus raised this point about the market prices and I understand maybe, Secretary Koh, you tried to answer this for him. I just want to be clear. Do either one of you have any thoughts as to why you get to the point where there is a limited number of manufacturers of a particular generic, why the prices at that point remain low? I mean the market should be able to work—the market of supply and demand and obviously when a brand name drug, which is very expensive, first goes generic and you have several manufacturers jumping in an producing that generic at a much, much lower price, and then finally it gets too low for some of them to survive, they stop doing it and go on to something else, maybe another generic and a couple or maybe even one company hangs on. It would seem because of supply and demand that that company would be able to raise their prices. Are there any government rules, regulations, laws, pharmacy benefit managers, something that would cause them not to be able to raise their prices even though the market would certainly let them do that otherwise?

Mr. KOH. Yes, Congressman, so we have come to understand that this is a complex business situation where the standard economic principles of supply and demand do not easily apply. And we have manufacturers, we have purchasers, providers, hospitals, we have group purchasing organizations and pharmacy benefit managers, so we have multiple forces here all working to the final outcome that ordinarily you would see with a rise in pricing profit, but that doesn't apply here. So this is why we need the extra analysis that our department is doing and others and we welcome new informa-

tion and modeling to really help us understand the root causes better.

Mr. GINGREY. Dr. Kweder?

Ms. KWEDER. I think the questions that you raise are exactly some of the questions that we have as we really try to understand the roots of this problem. What are the things that could be done to try and prevent these shortages from occurring or even being at risk in the first place.

Mr. GINGREY. Well, I thank both of you for those answers because, you know, the Federal Government tries to do the right thing in many instances—I would hope in all instances and it seems that far too much of the time they screw it up. And so that is why I ask you those questions and I hope that you will continue to look at that so that market forces can continue to prevail. Then I don't think we would be faced with these shortages.

Mr. PITTS. The gentleman yields back? This is the round of questions for the subcommittee members. We have a couple of members of the committee who have joined us. The chair recognizes the gentleman, Mr. Walden, for 5 minutes for questions.

Mr. WALDEN. I thank the chairman very much, first of all, for his recognition since I am not a member of the subcommittee but also for having this hearing. And I appreciate the testimony from the 2 witnesses today. I got involved in this issue some time ago because of an oncology doctor in my district, Dr. Chuck Dibs, who brought this issue to my attention, my staff's attention. And the drug specifically that I recall he mentions was—and I will try and say this right—doxorubicin. Is that right? I understand it is an ovarian cancer drug which he has prescribed for a very long time, apparently a very effective drug. And I am not a doctor but that is what he tells me. What was the FDA's role in interrupting the production of that drug? Can you speak to that?

Ms. KWEDER. I can speak to that very generally. There were several companies that produced doxorubicin. One of them which was the major supplier also was the same producer for the cytarabine, APP, that Dr. Koh mentioned earlier. Some of the issues were exactly the same. There were facility issues, production delays because of, you know, chronic problems in an aging facility is probably the best way to summarize it. What FDA did was we worked with the other 2 producers to facilitate their ability to increase production. It did take a while. As I said, these are complex products to make. Companies can't just ramp up production overnight.

Mr. WALDEN. Right.

Ms. KWEDER. But in the meantime, a fourth company came in with a new version of the product and helped to make up the supply. So we make sure to expedite review of that fourth company's application and the inspections, et cetera, that were necessary in order to turn this around.

Mr. WALDEN. Now, Dr. Koh, do you have any comment on that?

Mr. KOH. I think Dr. Kweder summarized it well.

Mr. WALDEN. So you feel like you have taken all the steps? This drug is now available on the market again and without shortage? Is this accurate?

Ms. KWEDER. My expert tells me, yes. Yes, doxorubicin itself is. There is another version of the drug that is sort of a special formu-

lation that has a sole source that continues to be a problem, but again, that is a different company.

Mr. WALDEN. All right. I know, Dr. Koh, you mentioned glass and metal in injectables I think you were discovering which sends sort of shivers up everybody's spine. I have also heard though that with the new technologies, the scientists are able to see deeper into the drugs we had ever seen before in parts per billion or whatever. Again, this is your field, not mine. But are we looking deeper and finding things that we never knew was there before and is that really a problem from a health standard or is it a question that may play a role?

Mr. KOH. Well, again, those examples, Congressman, are very graphic examples on the quality issues that we are facing. I must say though that again the FDA has worked with companies so in the case of particulate matter—pieces of glass, pieces of metal—first to identify the issue but also there have been advances in developing filtering systems so we can filter those out and make those drugs then safe to inject into patients. So that is another example of regulatory flexibility that has marked this chapter of our history. So I guess the end of my time is about to expire but—I mean my time to ask questions is about to expire. I just want to clarify that.

It is this sense of urgency. I applaud you for bringing people together and trying to figure this problem out, but as I am hearing from both Dr. Dib and others in my district there is this, you know, patient comes in, the drug is not available, they have been prescribed it for years, it is effective, it works, and they can't get it. I know my own mother had ovarian cancer and died from it and so I have just this sense of patient urgency. I know you feel that, both of you. We all do. And so if there is a way we can play a constructive role here, whether it is Ms. DeGette's bill on notification, I mean she has put a lot of work into this. You know, we just need to do everything we can to be a partner in this to find a solution. I look forward to working with both of you and members of this committee to the extent they will let me play a role. So with that, I would yield back the balance of my time.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentlelady from Colorado, Ms. DeGette, for 5 minutes for questions.

Ms. DEGETTE. Thank you very much. And I want to thank my colleague from Oregon for the free commercial announcement.

Mr. Chairman, thanks for letting me participate. It is good to be back in my old stomping grounds of the House subcommittee. As I know you have been discussing, Congressman Rooney and I have introduced in a bipartisan way the Preserving Access to Lifesaving Medications Act, which creates an early warning system between FDA drug companies and providers so that we can respond to these drug shortages quickly and efficiently. Do I think that this bill will solve the root problems of the drug shortage crisis? No. But do I think it is a necessary first step? Absolutely. And I appreciate the witnesses coming here to talk to the members of this committee.

This bill came up because Mr. Rooney and I independently were going around meeting with our hospitals and our doctors and suddenly, they started saying to us, you know, I was in the middle of a chemotherapy treatment of a child and suddenly I couldn't get

the drug. And I am sure it didn't happen immediately but it seemed like it did. Doctor, you are shaking your head. Do you want to comment on that?

Ms. KWEDER. Well, to the prescriber, you know, they are not following, you know, Web sites. They just know that they can't get the drug and they have a patient who is ill and needs it today or tomorrow and not in 2 months when the supply can be re-upped, and that is a very difficult position to be in as a physician and even worse as a patient.

Ms. DEGETTE. And is there some reason why these shortages have increased recently? Either one of you?

Ms. KWEDER. We are trying to understand that. Some of the things that we have identified is that these are products that are complicated. Most of the products that have been problematic are complicated to produce, there are a limited number of producers, and many of them are working in facilities that are aging and have had chronic challenges in maintaining production or product quality.

Ms. DEGETTE. Yes. And you know, I think before I got here, Mr. Chairman, you had discussed the current reporting system, which is the reporting system for companies that don't have competition and it is a voluntary system. Even though it is much more limited, it has really worked. In 2010, 38 drug shortages were avoided when the Agency was given advance notice. And I just want to give a couple of examples. In August of 2009, Hospira notified FDA of their intention to discontinue the drug potassium phosphate in 2010 due to low volume. The drug is often critical for neonatal care. Hospira received a note back from the FDA drug shortage in September 2009 thanking them and then in March 2011 the other supplier of potassium phosphate, American Regent, recalled its product because of a quality issue. So what happened then is in April 2011, the FDA made Hospira aware of the drug shortage caused by the recall and asked them to assess their ability to return to manufacturing. And then in that same month, Hospira told the Agency that they would return to manufacturing potassium phosphate so that the patients could be served. And so it worked. But that is on a very limited basis. And so I just think that this could really work.

And I guess I want to ask you, Dr. Koh, in my minute remaining, how will it work if we enact legislation like this to get the information into the providers' hands that there is an impending drug shortage? Because you folks have had some experience with it.

Mr. KOH. Sure. And Congresswoman, first of all, thank you for your leadership on this issue. It is very, very much appreciated. And we all feel that establishing the highest level of communication as early as possible about any potential shortage could give us the opportunity all to be proactive. And that is not just FDA and HHS but also providers and hospitals and patients. So if we can do this together, understand that a potential shortage is on the horizon as soon as possible, make that information available to relevant parties and ultimately to patients and the public, then we can all work together in a proactive way.

Right now we are in a situation that you have summarized very well where the reporting is voluntary. Oftentimes the FDA does not know until too late and then patients are stuck in this dire situa-

tion, which is just not acceptable. So we are looking forward to greater emphasis on early notification and communication.

Ms. DEGETTE. Great. Thank you so much, Mr. Chairman. My time has expired.

Mr. KOH. Thank you, Congresswoman.

Mr. PITTS. The chair thanks the gentlelady.

Before we go to Panel 2, we have one request for a follow-up for Panel 1. Without objection, we will let Dr. Cassidy ask that follow-up question.

Mr. CASSIDY. Thank you. My office had looked into I think maybe it had been cysteine. And there was a problem that we heard back from you of endotoxin being in the product and it was unclear where in the manufacturing process that endotoxin had been introduced. Now, obviously that is an issue and frankly, I called my constituent. I said FDA did the right thing. We don't know whether endotoxin was introduced. It is very disturbing to me that endotoxin should be in the product so we are kind of euphemistically speaking about manufacturing problems but really they are significant. So is it a pattern? And when we are saying manufacturing that know there is actually some sort of contamination such as endotoxin for which in their GMP they do not know where it is entering. Because that is a process problem that is of tremendous concern.

Ms. KWEDER. The answer is yes. That is exactly the kind of thing that we are concerned about. When you find end product that has endotoxin in it, the first thing one needs to do is figure out how that endotoxin is getting in there in the first place. And there are multiple steps in production where that could be occurring and figuring it out is not easy and it can take a very long time to determine that and then a long time to fix it. And particularly we see this with metal shavings in medicine, glass shards in vials, all things that would be unconscionable to give to patients. But the key is being on top of those good manufacturing practices and maintaining facilities to avoid those kinds of events. And where you have facilities that are in 100 percent production mode all of the time, it is often difficult to maintain your facilities and modernize them in a way for a company to assure that they are producing a reliably high-quality product.

Mr. CASSIDY. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman. I believe Mr. Pallone has a follow-up as well.

Mr. PALLONE. Dr. Koh, as Mr. Shimkus said earlier, classic economics would suggest that when a product is in demand, prices should rise and the market establish a new equilibrium, yet we are now in the seventh consecutive year with more shortages than the year before. I am also curious why the market has failed to establish an equilibrium because both Mr. Shimkus and Mr. Guthrie discussed public program pricing constraints, and as I understand these constraints, they apply to brand name drugs and not generics. Is that correct that they only apply to the name brand and not generics?

Mr. KOH. Well, Congressman, those economic issues are precisely the ones that we are analyzing right now. And we have especially our assistant secretary for planning and evaluation and health

economists looking at the economic principles and the modeling that could help us predict where we need to go in the future. So thank you again for raising these issues. These are very, very complicated business and economic models we have come to find.

Mr. PALLONE. The generic drugs are where we have seen most of the drug shortages in recent years.

Mr. KOH. That is right.

Mr. PALLONE. I mean if there is that distinction, is that the problem?

Mr. KOH. Well, we do know that is it older generic sterile injectables that are making up about 3/4 of these shortages. And so that is where we are indeed focusing our attention.

Mr. PALLONE. I don't know if either Mr. Shimkus or Mr. Guthrie asked you if you said you were going to get back to them, but, you know, I would really like to get some answers, you know. I mean obviously you are not prepared or you don't feel you have an answer today, but I would like you to get back to us through the chairman if you could.

Mr. KOH. I would be happy to, Congressman. So again I did mention we have an upcoming report from the FDA that is going to give further economic analyses that are also intensely underway right now.

Mr. PALLONE. Is that going to relate to this or you don't know for sure?

Mr. KOH. Hopefully we will get a better understanding of root causes.

Mr. PALLONE. Mr. Chairman, if he could get back to us on that because I know many of us have sort of asked the same question and I would really like to know.

Mr. KOH. Sure. Thank you.

Mr. SHIMKUS. If the chairman would yield just on this point.

Mr. PITTS. Go ahead.

Mr. SHIMKUS. And I thank my friend for following up on this debate and this question. But in my opening statements, I didn't just focus on the government pricing. I did say insurers, too, so I mean we are all kind of in this together and the market going to work it has got to work. So I just wanted to just correct the record. I wasn't just picking on——

Mr. PALLONE. Oh, no, I understand. I just wanted to bring up the public program aspect. Whenever, you know, you can get back to us on it because I think, you know, I mean I understand to be perfectly honest, I mean a lot of the questions that we have asked today we have gotten a response and we have a little better idea, but I almost feel like more questions have been raised than answered today. And that is not anybody's fault but that is kind of where I feel we are right now, Mr. Chairman.

Mr. PITTS. All right, thank you. If you will respond to the questions in writing, we will get those to the committee members——

Mr. KOH. Thank you, Chairman.

Mr. PITTS [continuing]. And I look forward to reading your report. The chair thanks the first panel for your——

Mr. KOH. Thank you very much.

Mr. PITTS [continuing]. Testimony. Thank you. We will call at this time Panel 2. And our second panel consists of 7 witnesses.

Our first witness is Mr. Jonathan Kafer, Vice President of Sales and Marketing for Teva Health Systems and testifying on behalf of Teva Pharmaceuticals. Next is Mr. John Gray, the President and CEO of Healthcare Distribution Management Association. Our third witness is Kevin Colgan. He is the corporate director of pharmacy at Rush Medical Center in Chicago. Our fourth witness is Mr. Mike Alkire, Chief Operating Officer of Premier, Inc. Next, we will hear from Dr. Charles Penley, who is testifying on behalf of the American Society of Clinical Oncology. We also have Mr. Richard Paoletti, the Vice President of Operations at Lancaster General Health. And finally Dr. Robert DiPaola, Director of the Cancer Institute of New Jersey.

We thank all of you for coming. Your written testimony will be entered into the record. We ask that each of you would summarize your testimony in 5-minute opening statements.

And Mr. Kafer, you may begin your testimony.

STATEMENTS OF JONATHAN M. KAFER, VICE PRESIDENT, SALES AND MARKETING, TEVA HEALTH SYSTEMS; JOHN M. GRAY, PRESIDENT AND CEO, HEALTHCARE DISTRIBUTION MANAGEMENT ASSOCIATION; KEVIN J. COLGAN, CORPORATE DIRECTOR OF PHARMACY, RUSH UNIVERSITY MEDICAL CENTER, ON BEHALF OF AMERICAN SOCIETY OF HEALTH–SYSTEM PHARMACISTS; MIKE ALKIRE, CHIEF OPERATING OFFICER, PREMIER, INC.; W. CHARLES PENLEY, CHAIR, GOVERNMENT RELATIONS COMMITTEE, AMERICAN SOCIETY OF CLINICAL ONCOLOGY; RICHARD PAOLETTI, VICE PRESIDENT, OPERATIONS: PHARMACY, LABORATORY, AND RADIOLOGY, LANCASTER GENERAL HEALTH; ROBERT S. DIPAOLA, DIRECTOR, CANCER INSTITUTE OF NEW JERSEY

STATEMENT OF JONATHAN M. KAFER

Mr. KAFER. Thank you, Chairman. Chairman Pitts, Ranking Member Pallone, and distinguished colleagues within the subcommittee and full committee, thank you very much for the opportunity to be here today. As referenced by the chairman, my formal testimony has been submitted to you. I am more than willing to answer questions specific to that testimony throughout the questioning period and I will summarize my remarks in my opening.

I am John Kafer. I am vice president of sales and marketing for Teva Health Systems, representing Teva Pharmaceuticals. Teva Pharmaceuticals is a global leader in brand, generic, and biologic pharmaceutical products. We are a market leader in many of the markets in which we serve. Here in the United States, we are the market leader in generic products. We have a vast portfolio including many dosage forms, including oral solid presentations, injectable presentations, including a significant portfolio of oncology generic injectable presentations, and I look forward during the questions period to share some insights specific to that very important category.

As referenced, we are a market leader. Teva is a market leader and we understand and embrace the responsibility that does come with being a market leader, and in that context, I am very happy to be here today.

One side note, as all of us have been, we all have personal stories as it relates to family, friends, people we know, individuals that have been impacted by not being able to get medications. In my particular situation, I have friends and family as well. Given the role I play, they reach out to me hoping I may be able to make a difference. Unfortunately, there is many times I can't and it is very challenging. At the same time, given the role I play, I hear from patients, I hear from family members of patients, I hear from constituents, I hear from physicians looking to the manufacturer to ask the question, "Why?" And we respond and we certainly understand that.

And at the same time, I see every day when I go to work hundreds and hundreds of people working tirelessly around the clock, sparing no expense to do whatever we can to return to historical production volumes so that we can get these critical products back to market.

As referenced in earlier testimony, this is a very complex multi-stakeholder issue and it is going to require the coordination and communication amongst all those stakeholders in order for us to resolve this issue. As noted in earlier testimony as well, there are many factors that impact the drug shortage issue, whether it be API being sourced and available. We have discussed that. The industry has experienced manufacturing challenges. I will go into greater detail specific to how it impacts a sterile facility versus an oral solid facility. And there has been regulatory impacts on facilities.

As appropriate and as required, the FDA regulates these complex facilities and these products to assure that the manufacturing community is operating within full CG&P compliance, ultimately to provide the highest quality of products to all of us in this room. We understand that and, as a manufacturer, we certainly embrace that.

Most of the shortages, however, are unanticipated. Those unanticipated shortages can have boomerang effects up and down the supply chain. And as noted in earlier testimony, as we will get into in greater detail, there are a handful of manufacturers that sometimes are unable to pick up the lost supply from another manufacturer, and we will go into detail around that as well.

What is Teva doing specifically to address some of the drug shortage issues? We have made a significant investment in enhancement of our facilities as well as our quality systems. We have unrestricted access to our resources globally to prioritize those people in those facilities that require the work that needs to be done to get the products back to market. We have embarked on a very aggressive redundancy plan. There is no requirement to a manufacturer to have a secondary or tertiary facility qualified to manufacture these products. We have identified, in combination with drug shortage division, those most critically medically necessary products and we have 5 FDA-approved facilities and we have put a team in place that is actively working on redundancy planning for these critical products.

As referenced also from the testimony of Dr. Kweder and Dr. Koh, there has been extraordinary collaboration within the FDA branches as it relates to resolving and mitigating these challenges.

I can speak to a couple of different references. 1) There was a discussion earlier in testimony around coordination of importation of products to alleviate critical drug shortages. There was a specific instance in which we worked with the FDA to bring in a product called leucovorin that is used in combination with chemotherapy twofold to enhance the effectiveness of that treatment as well as to mitigate side effects. We brought it in, we had a significant amount of resources to work collaboratively with that, and we were able to help mitigate that problem.

The solutions that we are looking at, recognizing it is a multi-stakeholder issue, I do need to comment that as it exists today, there is tremendous cooperation within the drug shortage group and the manufacturing community. As referenced earlier, there is no formal process. It is an informal process. And I can speak on behalf of Teva and the other leading manufacturers in this space that we do all collaborate with the FDA, as testified earlier, and we take that very seriously and we are responding where we can. The doxorubicin example mentioned earlier, I received a phone call from York shortage, do what we can. We were able to work in collaboration with them and get product released to market and we continue to prioritize those types of products.

During questioning, I would be more than happy to go into greater detail around how we are seeing the coordination and the effectiveness and how we would like to see a greater communication amongst multiple stakeholders beyond the manufacturer and FDA. Going forward, we had seen discretion by the Agency deployed to allow earlier available of key products. That is working. We would like to see a process in which we can get that on the front end as well to potentially mitigate potential problems while incorporating remedial steps that have no impact or concern to the patient.

I know I am over my time share, so I apologize.

[The prepared statement of Mr. Kafer follows:]

SUMMARY:
TESTIMONY OF JONATHAN M. KAFER,
VICE PRESIDENT SALES & MARKETING, TEVA HEALTH SYSTEMS,
TEVA PHARMACEUTICALS

- Teva is a world leader in brand, generic, and biologic pharmaceutical products. We are proud to manufacture life-saving and life-changing medicines that are in nearly every medicine cabinet in America. Every minute 1,203 prescriptions are filled with Teva products.

- Drug shortages are a complex and multi-stakeholder issue and it is incumbent on active ingredient suppliers, generic and brand manufacturers, wholesalers and distributers, health care providers, and government agencies to work together to resolve this issue.

- There are many factors that impact the availability of critical drugs within the supply chain. Factors that lead to significant shortages are most often due to unanticipated events that can create an immediate impact on availability.

- Despite the challenges, Teva makes every possible effort to supply patients with needed medicines including making significant investments and enhancements to existing facilities and quality programs.

- Increasing communications across stakeholders would mitigate and help resolve shortages. From the time of the initial filing of the application through the ongoing compliance and review process, it is imperative that the communication between the manufacturing facility and the FDA is one that enables visibility amongst all parties.

- Drug shortages are resolved more quickly if there is an expedited review to qualify new manufacturing facilities and API suppliers as well as pending Prior Approval Supplements (PAS's) (as is taking place at this time within an informal fashion).

- To address shortages that involve controlled substances the FDA Center for Drug Evaluation and Research divisions and the Attorney General should establish a process that would streamline manufacturing production quotas in response to drug shortages.

TESTIMONY OF

JONATHAN M. KAFER

VICE PRESIDENT SALES & MARKETING, TEVA HEALTH SYSTEMS

TEVA PHARMACEUTICALS

EXAMINING THE INCREASE IN DRUG SHORTAGES

BEFORE THE

U. S. HOUSE REPRESENTATIVES
COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON HEALTH

SEPTEMBER 23, 2011

Good morning Chairman Pitts, Ranking Member Pallone and Members of the Subcommittee. Thank you for giving me an opportunity to discuss the critical issue of drug shortages.

I am Jonathan Kafer, Vice President of Sales and Marketing for Teva Health Systems, and I am here today on behalf of Teva Pharmaceuticals. Teva is a world leader in brand, generic, and biologic pharmaceutical products. We are proud to manufacture life-saving and life-changing medicines that are in nearly every medicine cabinet in America. Every minute 1,203 prescriptions are filled with Teva products. It is our highest priority to provide quality medicines to those who need them. Any drug shortage or lack of access to our products is contrary to our mission as a company and is met with immediate action. In my remarks I would like to shed some light on why drug shortages are occurring, discuss what Teva is doing to ensure patient access, and offer some solutions to help avoid future drug shortages.

Current Landscape

As the Subcommittee is well aware, the list of drugs in short supply is growing longer, and more and more patients do not have access to the pharmaceutical products that they have relied on for many years. Drug shortages are a complex and multi-stakeholder issue, and it is incumbent on active ingredient suppliers, generic and brand manufacturers, wholesalers and distributers, health care providers, and government agencies to work together to resolve this issue.

Causes of Drug Shortage

There are many factors that impact the availability of critical drugs within the supply chain. Factors that lead to significant shortages are most often due to unanticipated events that can create an immediate impact on availability.

In order to maintain a consistent supply of pharmaceuticals, it is imperative for a manufacturer to have a qualified and reliable source of active pharmaceutical ingredient (API). The qualification process to identify an appropriate API supplier for any drug product can be a very onerous one. To qualify and gain FDA approval for a new API supplier or alternate manufacturing site for an already approved supplier can take as long as 2 – 3 years. Because this process is so lengthy, many drugs have only one API supplier and one manufacturing site approved in their applications. If, for any reason, the API supply is insufficient, i.e., there is a sudden increase in demand for the product or there are difficulties encountered at a particular manufacturing site, a drug shortage can easily be the outcome.

These same circumstances can impact supply indirectly as they can create unanticipated forecast demands on the remaining manufacturers to increase production levels to cover the shortfall. This dynamic is particularly challenging if the product is a controlled substance. From our work with the DEA and FDA, we know that it is a difficult balancing act to ensure availability of controlled substances to patients in need while also striving to curb abuse and diversion. In an effort to control the supply of these medicines, the DEA makes yearly allocations of controlled drugs to the respective

manufacturers of these products. In many instances, however, the use of a drug product changes over the year due to increased usage or shifting of markets. This can result in a shortage of these products, because without access to more of the controlled active ingredient, manufacturers are unable to increase supply. Currently, there are a number of controlled drugs on the American Society of Health-System Pharmacists (ASHP) shortage list.

Many life-saving therapies that are experiencing shortage are injectable products. Although several of these medicines have been available to the public for decades, they are complex and require specialized facilities. As appropriate, the FDA closely regulates these products and facilities and continues to require updated product specifications and other manufacturing requirements in order to maintain the highest quality standards for these products. Although the number of manufacturers that produce injectable medicines has increased over the past several years, the specialized nature of the products and facilities necessary limits the number of producers available to ease a drug shortage.

Whether a shortage is the result of a short supply of ingredients or from manufacturing difficulties at a single manufacturer, the fundamental problem that we encounter is that it can take a considerable amount of time to correct a shortage or increase production of a product.

What Teva is Doing to Increase Access

Despite the challenges, Teva continues to make every possible effort to supply patients with needed medicines including making significant investments and enhancements to existing facilities and quality programs. We have worked closely in conjunction with FDA to alleviate shortages. To better understand how we work closely with the FDA, I'd like to share with you the steps we have taken to alleviate shortages for the product Leucovorin. Leucovorin is an injectable drug that is given to patients receiving chemotherapy to protect them from negative side-effects and improve the effectiveness of the cancer treatment. The market experienced a shortage of this product when all three manufacturers of leucovorin, including Teva, experienced short and long term supply challenges. Teva, in conjunction with the FDA, worked to provide a temporary importation of the European Union (EU) approved Leucovorin Calcium Folinate Solution for Injection to the United States market to address the current shortage. While there is still much work to be done in order to ensure all patients in need of this product have access, this example does illustrate the efforts that have been made by both Teva and the FDA to communicate with one-another and develop workable solutions for the benefit of patients.

Potential Solutions

As I said at the beginning of my testimony, this is a multi-faceted problem that involves a number of stakeholders. Not surprisingly, there is no silver bullet solution. In order to

adequately address drug shortages, more than one solution will be required. For example, it is important to improve the avenues of communication so that shortages can be averted or, at least, solutions can be more readily implemented. From the time of the initial filing of the application through the ongoing compliance and review process, it is imperative that the communication between the manufacturing facility and the FDA is one that enables visibility amongst all parties. If an enforcement action is proposed or contemplated that would significantly curtail the manufacturing capability of a major supplier of critical drugs, the long-term effect of that action should be discussed among the affected manufacturers, the FDA regulators (FDA's Office of Compliance and FDA's Office of Regulatory Affairs) and FDA's Drug Shortage Team before the action is taken. Having the opportunity to discuss the compliance issues with the inspectors during and after the inspection will greatly assist the industry in both resolving the issues and as well as expediting the remediation of the site with minimal impact to the production of products whose supply could be negatively impacted.

When drug shortages do occur, expedited review to qualify new manufacturing facilities and API suppliers, e.g. expediting pending Prior Approval Supplements (PAS's), greatly speeds the reintroduction of products back to the market. This is occurring to some extent currently, however, steps could be taken to establish a more formal process through the revision of current regulations and guidances .

One strategy manufacturers employ to maximize the utilization of capacity and assure an adequate supply for patients is to transfer products to other manufacturing locations. For U.S. supply, approval for new facilities requires a PAS, an inspection and a

triggering submission, and under routine circumstances may take up to 24 months. In other highly regulated markets, such as Europe, this can be done with notification to local authorities upon operational readiness, and generally would be approved immediately following inspection of such facilities. Approval for additional technologies at an already approved facility (example adding capsule manufacture and packaging) requires a PAS in the U. S. In contrast, this can be done with no additional regulatory approval in other regions. FDA should re-evaluate the regulations and guidances relating to these changes and make revisions that would more easily accommodate these changes.

For shortages that involve controlled substances and DEA quota of active ingredients, one proposed solution is to require collaboration between the FDA Center for Drug Evaluation and Research divisions and the Attorney General to establish a process that would streamline manufacturing production quotas in response to drug shortages of controlled substances. In this way the cessation of production by one manufacturer triggers the timely transfer of quota to another manufacturer in order to maintain a steady supply of product in the market. The multiple government Centers, Offices, and Agencies with responsibility for the approval, compliance and control of drugs should be required to regularly communicate and coordinate activities such that any action taken does not leave medications in short supply. Shortages must be avoided where possible and alleviated in an expedited manner.

Conclusion

In conclusion, Mr. Chairman, Teva will continue to work closely with FDA and Congress to solve drug shortages when they occur and to prevent future shortages.

Thank you. I would be happy to address any questions the Subcommittee may have.

Mr. PITTS. The chair thanks the gentleman. Mr. Gray, you are recognized for 5 minutes.

STATEMENT OF JOHN M. GRAY

Mr. GRAY. Good morning, Chairman Pitts, Ranking Member Pallone, and the members of the Energy and Commerce Subcommittee on Health. I am John Gray, President and CEO of the Healthcare Distribution Management Association, Arlington, Virginia. I appreciate the opportunity to come here today, provide some overview of the pharmaceutical distribution system and inform your committee on efforts regarding some critically important issue around drug shortages.

A little history—HDMA is a national association representing America's primary healthcare distributors, a vital link in our Nation's system of healthcare distribution. Each business day, our 34-member companies ensure that nearly 9 million prescriptions, medicines, and healthcare products are delivered safely and efficiently to nearly 200,000 pharmacies and clinics, hospitals, nursing homes, and other providers nationwide. Approximately 90 percent of all pharmaceutical product sales in the United States flow through our member companies. Continuous innovation and operation efficiency have really set our members apart in trying to annually contribute an estimated about $42 billion in value to the Nation's healthcare system.

Now, Federal law defines wholesale drug distribution as "the distribution of prescription drugs to other than the consumer or patient." Wholesale distributors are licensed entities that are bound by a range of Federal and State laws. In addition, our distributors must comply with licensure requirements in every State in which they operate.

It is important to note HDMA members are primary distributors. I said that earlier; I will reiterate it. But they buy predominantly from pharmaceutical manufacturers and sell only to appropriate licensed customers, the vast majority of which are pharmacies or healthcare providers.

Pharmaceutical products are distributed through a highly coordinated supply chain in this country to provide maximum efficiency and effectiveness and safety. Pharmacies and other healthcare entities generally place orders for prescription medicines by 8 o'clock in the evening and receive deliveries from their distributors the next morning. The average distribution center in this country processes nearly 2,000 orders a day. On the average, a warehouse maintains about 30 days of inventory level. This number varies by product, is subject to demand, seasonality, cost, and other factors. Pharmaceutical products with special handling requirements typically have shorter cycle times in the system.

Distributors provide an array of services for manufacturers beyond simply the movement of product, including but not limited to receivables risk management for the manufacturer, customer validation, order management, inventory management tracking, processing returns and recalls, and contract management. For pharmacy and provider customers, our distributors provide an equal array of services, including aggregate ordering, assistance with stocking needs, support for information systems and software, as

well as accounting and credit support. In the case of inventory management, distributors are able to fill customer orders 6 or 7 days per week, 365 days a year, which limits the need for large inventory levels at the pharmacy level.

In sum, distributors serve to maximize the efficiency between manufacturers and healthcare providers by managing a very complex network of products of systems by efficiently providing mechanisms for this seamless transformation of information and product.

Through the unique position of distributors and our close relationship with all the stakeholders, we are acutely aware of the impact of drug shortages on patients. Effectively addressing the drug shortage is difficult and complex for the entire healthcare community in large part because the shortage typically appears with little or no warning and often requires significant resources to manage. HDMA and our member companies work hard to improve the communications within the supply chain from manufacturer to distributor to provider where possible and try to mitigate the impact of the drug shortage.

Although distributors do not manufacture product, they do play an important role in helping to coordinate and share information about drug shortages when those shortages arise. Distributors are typically notified of a shortage by a manufacturer or a provider partner. Once that shortage information is received, distributors communicate with their manufacturer partners about product availability to understand the scope and expected duration of any shortage. Then the distributor works as quickly as possible with customers to fill orders to the extent they are able to do so based upon purchasing history or, if necessary, to identify alternative products in the supply chain. So as you can appreciate, there is a delicate balance between the need to share information at the appropriate level, but at the same time preventing an environment for panicked buying.

HDMA has worked collaboratively with the American Society of Health System Pharmacists, Federal agencies and the Congress, and other supply chain partners to share expertise about the whole drug supplies chain. In addition, we are working with our distributor members and manufacturer providers to update voluntary industry guidelines on improving communications between supply chain partners in the event of shortages. We hope this effort will contribute to the better management of the process in its entirety.

HDMA strongly believes the healthcare industry as a whole, the government, and stakeholders must continue to work together towards some collaborative solutions of this problem that mitigate the impact of the shortages, and most importantly, the impact on the key stakeholder—the patient. To that end, I thank you again for this invitation to participate and I hope the overview has been valuable. And I look forward to your questions.

[The prepared statement of Mr. Gray follows:]

ONE PAGE SUMMARY

Testimony before the
House Energy and Commerce Committee
Subcommittee on Health
United States House of Representatives
September 23, 2011

John M. Gray, President and CEO, Healthcare Distribution Management Association

The pharmaceutical distribution industry provides a vital link in our nation's healthcare delivery system.

The health care industry as a whole should work together to develop collaborative solutions that mitigate the impact medication shortages have on the most important stakeholder: the patient.

Although distributors do not manufacture product, they do play an important role by helping to coordinate and share information about drug shortages when they arise.

In the event of a shortage, there needs to be a balance between the need to share an appropriate level of information while, at the same time, preventing an environment for "panic buying" which could further exacerbate the shortage.

HDMA's members are primary distributors – they buy predominately from pharmaceutical manufacturers and sell only to appropriately licensed customers, the vast majority of which are pharmacies and other healthcare providers.

Testimony before the

House Energy and Commerce Committee

Subcommittee on Health

United States House of Representatives

September 23, 2011

John M. Gray, President and CEO

Healthcare Distribution Management Association

Testimony before the Subcommittee on Health
Committee on Energy and Commerce
United States House of Representatives

Statement of
John M. Gray, President and CEO
Healthcare Distribution Management Association
September 23, 2011

Good morning Chairman Pitts, Ranking Member Pallone and Members of the Energy and Commerce Subcommittee on Health. I am John Gray, president and CEO of the Healthcare Distribution Management Association (HDMA). Thank you for the opportunity to provide an overview of the pharmaceutical distribution system and to inform the Subcommittee's efforts regarding the critically important issue of drug shortages.

HDMA is the national association representing America's primary healthcare distributors – the vital link in our nation's healthcare system. Each business day, HDMA's 34 member companies ensure that nearly nine million prescription medicines and healthcare products are delivered safely and efficiently to nearly 200,000 pharmacies, hospitals, nursing homes, clinics and others nationwide. Approximately 90% of all pharmaceutical product sales in the United States flow through HDMA distributor members. Continuous innovation and operational efficiency have

allowed our members to annually contribute an estimated $42 billion in value to the nation's healthcare system.

Federal law defines wholesale distribution as the "distribution of prescription drugs ... to other than the consumer or patient." Wholesale distributors are licensed entities that are bound by a range of federal and state laws. In addition, distributors must comply with the licensure requirements of each state in which they operate. It is important to note that HDMA's members are considered primary distributors – they buy predominately from pharmaceutical manufacturers and sell only to appropriately licensed customers, the vast majority of which are pharmacies and other healthcare providers.

Pharmaceutical products are distributed through a highly coordinated supply chain that is designed to provide maximum efficiency. Pharmacies and other healthcare entities generally place orders for prescription medicines by 8 p.m. in the evening and receive deliveries from their distributors the next morning. The average distribution center processes 1,965 orders daily. On average, warehouses maintain 30-day inventory levels. This number varies by product and is subject to demand, seasonality, cost and other factors. Pharmaceutical products with special handling requirements typically have shorter cycle times.

Distributors provide an array of services for manufacturers beyond the movement of product, including but not limited to receivables risk management, customer validation, order management, inventory management tracking, processing returns and recalls, and contract management. For pharmacy and provider customers, distributors provide an equal array of services including aggregate ordering, assistance with stocking needs, support for information systems and software, as well as accounting and credit support. In the case of inventory management, distributors are able to fill customer orders six or seven days per week, which limits the need for large inventories at the pharmacy level.

In sum, distributors serve to maximize efficiencies between manufacturers and healthcare providers by managing a complex supply network and efficiently providing a mechanism for seamless interaction.

Through the unique position of distributors and their close partnerships with all of the stakeholders across the supply chain continuum, they are acutely aware of the impact of drug shortages, especially on patients.

Effectively addressing a drug shortage is a difficult and complex challenge for the entire healthcare community, in large part because a

shortage typically appears with little or no warning and often requires significant resources to manage.

HDMA and our member companies are working hard to improve communications within the supply chain and, where possible, to mitigate the impact of drug shortages.

Although distributors do not manufacture product, they do play an important role by helping to coordinate and share information about drug shortages when they arise. Distributors are typically notified of a shortage by a manufacturer or provider partner. Once information is received, distributors communicate with their manufacturer partners about product availability to understand the scope and expected duration of any shortage. They then work as quickly as possible with their customers to fill orders, to the extent they are able, based on purchasing history or, if necessary, to identify alternative product options. As you can appreciate, there is a delicate balance between the need to share an appropriate level of information while, at the same time, preventing an environment for "panic buying."

HDMA works collaboratively with the American Society of Health-System Pharmacists, federal agencies, the Congress and other supply chain partners to share expertise about the drug distribution system. In

addition, HDMA is working with its distributor members, along with manufacturers and providers, to update voluntary industry guidelines on improving communication between supply chain partners. We hope this effort will contribute to the better management of product issues in the future.

HDMA strongly believes that the healthcare industry as a whole, the government and stakeholders must continue to work together toward collaborative solutions that mitigate the impact drug shortages have on the most important stakeholder: the patient. To that end, I thank you again for the invitation to participate in this hearing and hope this overview was valuable to the Subcommittee as it explores this important and timely topic.

Mr. PITTS. The chair thanks the gentleman. Mr. Colgan, you are recognized for 5 minutes for an opening statement.

STATEMENT OF KEVIN J. COLGAN

Mr. COLGAN. Good morning and thank you, Chairman Pitts, Ranking Member Pallone, and distinguished members of the subcommittee, for holding this hearing. My name is Kevin Colgan. I am the corporate director of pharmacy at Rush University Medical Center in Chicago, Illinois. I am here today because I cannot serve my patients or the caregivers due to shortages of medications, some of them critical to patient care.

While there is no single solution that will immediately solve the problem of drug shortages, there are things we can do to help address this issue. First, bipartisan legislation in both houses of Congress would enable FDA to require that drug manufacturers report confidentially to the Agency when they experience an interruption in the production of their product. This early warning system will help the FDA work with other manufacturers to ramp up production when another company experiences a problem. Moreover, the bills call upon FDA to work with manufacturers to develop continuity of supply plans which could help to identify backup sources of active pharmaceutical ingredients and produce redundancies in inventory to serve as reserve supplies.

While some have argued that this legislation won't have any impact, we disagree. You have already heard this morning from the FDA that in 2010, 38 drug shortages were avoided, and last year, 99 drug shortages were avoided when the Agency was given advance notice. Further, opponents of this approach argue that it will lead to hoarding. We know that hoarding already occurs. How do some find out about shortages before others? We don't know all the answers to this question. What we do know is that early warning to FDA will help make sure that everyone has the same information at the same time. Simply put, the public benefit of an early warning system far outweighs the risk of hoarding. In other emergency preparedness areas such as bioterrorism, flu pandemic, and natural disasters, we develop action plans and communication channels among necessary responders. Why would we approach drug shortages any differently?

Second, health-system pharmacists have been collaborating with other clinicians and members of the supply chain to work with the FDA to address this problem. For example, we believe FDA should have and devote necessary resources to speed up the regulatory process to address drug shortages. Other alternatives include improved communication between FDA field personnel and the drug shortages program to assess the comparative risk of public harm when a potential enforcement action will cause or worsen a drug shortage; exploring incentives for manufacturers to continue or to re-enter the market; a generic user fee program to speed approvals; and last, ensuring the Agency has the funding it needs to carry out its mission.

Many of you sitting in this room sometime over the next several months is going to receive the news that you, a family member, or a friend has been diagnosed with cancer, needs surgery, has been admitted to an intensive care unit, has a serious infection that re-

quires an IV antibiotic or antiviral medication, or has a premature baby or grandbaby that requires nutritional support. And the last thing you want to hear is that we don't have first-line medication therapy to treat you; that the medication we have may not work as well and could cause heart damage, but it is all we have to offer; or that we are delaying your treatment until we are able to obtain drugs that are in short supply. These are all situations, I, my clinical pharmacy staff, and the physicians, nurses, and respiratory therapists that we work with have had to manage over the past year. From our perspective, drug shortages represent a national healthcare crisis. We don't have one single solution, but we have offered a number of solutions that together can help resolve this problem.

Again, thank you Mr. Chairman, ranking member, and all members of the committee for the opportunity to provide input on this problem. Thank you.

[The prepared statement of Mr. Colgan follows:]

House Energy and Commerce Committee
Subcommittee on Health

Hearing:

Examining Drug Shortages

September 23, 2011

Statement for the Record
Submitted by the

American Society of
Health-System Pharmacists

American Society of Health-System Pharmacists
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Summary

Good morning and thank you Chairman Pitts, Ranking Member Pallone, and distinguished Members of the Subcommittee, for holding this hearing. My name is Kevin Colgan and I am Corporate Director of Pharmacy at Rush Medical Center in Chicago, IL. I am here today because I cannot serve my patients or their caregivers due to shortages of medications, some of them critical to patient care.

While there is no single solution that will immediately solve the problem of drug shortages, there are things we can do to help address the issue. First, bipartisan legislation in both houses of Congress would enable FDA to require that drug manufacturers report confidentially to the agency when they experience an interruption in the production of their product. This early warning system will help FDA work with other manufacturers to ramp up production when another company experiences a problem. Moreover, the bills call upon FDA to work with manufacturers to develop continuity of supply plans which could help to identify backup sources of API and produce redundancies in inventory to serve as reserve supplies. While some have argued that the legislation won't have any impact, we disagree. According to FDA, in 2010 38 drug shortages were avoided when the agency was given advance notice. Further, opponents of this approach argue that it will lead to hoarding. We know that hoarding already occurs. How do some find out about shortages before others? We don't know all the answers to this question.

What we do know is that early warning to FDA will help make sure that everyone has the same information at the same time. Simply put, the public benefit of an early warning system far outweighs the risk of hoarding. In other emergency preparedness areas such as terrorism, flu pandemic and natural disasters, we develop action plans and communication channels among necessary responders. Why would we approach drug shortages any differently?

Second, health-system pharmacists have been collaborating with other clinicians and members of the supply chain to work with FDA to address the problem. For example, we believe FDA should have and devote necessary resources to speed up the regulatory process to address drug shortages. Other alternatives include improved communication between FDA field personnel and the drug shortages program to assess the comparative risk of public harm when a potential enforcement action will cause or worsen a drug shortage; exploring incentives for manufacturers to continue or re-enter the market; a generic user fee program to speed approvals; and last, ensuring the agency has the funding it needs to carry out its mission.

Many of you sitting in this room sometime over the next several months is going to receive the news that you, a loved one or a friend, has been diagnosed with cancer, needs surgery, has been admitted to an intensive care unit, has a serious infection that requires intravenous antibiotics or antiviral medications, or has a premature baby or grandbaby that requires nutritional support. The last thing you want to hear is that we don't have first-line medication to treat you; that the medication we have may not work as well and

could cause heart damage, but it is all we have to offer; or that we are delaying your treatment until we are able to obtain drugs that are in short supply. These are all situations, I, my clinical pharmacy staff, and the physicians, nurses, and respiratory therapists that we work with have had to manage over the past year. From our perspective, drug shortages represent a national health care crisis. We don't have one single solution, but we have offered a number of solutions that together can help resolve this crisis.

Again, thank you Mr. Chairman, ranking member, and all members of the committee for the opportunity to provide input on this problem.

Drug Shortages Background and Policy Options

Shortages of prescription drugs in the United States have gained increasing attention in recent years due to the scope and severity of the drugs in short supply. The majority of these shortages occur in drugs that are generic injectables, often administered in a hospital or clinic setting. The shortages have been occurring for anti-cancer drugs,

anesthetics, pain, and nutritional drugs, all of which play crucial roles in the care of patients. The result of drug shortages is that caregivers must scramble to find the drug, or use an alternative if one is available. Many caregivers have expressed concern that even if an a therapeutic alternative exists, it is likely an older drug which may have more severe side effects or negatively interact with other medications the patient is taking. Further, drug shortages have caused widespread fear among caregivers who are deeply concerned that care could be delayed, rationed, or is provided in a suboptimal manner to stretch doses and preserve scarce supplies.

According to a study conducted in partnership between ASHP and the University of Michigan Health System, labor costs associated with managing drug shortages have an estimated annual impact of $ 216 million nationally, and more than 90% of respondents agreed that drug shortages were associated with an increased burden and increased costs today compared to two years ago.

Causes of drug shortages are many and complex. Manufacturing issues that lead to drug shortages include product quality issues that result in production halts or recalls, product discontinuations, and unavailability of active pharmaceutical ingredients (APIs) or other raw materials. Secondary shortages—or shortages that occur based on shifts in market demand caused by an initial shortage of another drug—are also common. Other contributing causes to drug shortages include quality issues that arise from the ever-increasing reliance on foreign ingredient and manufacturing sources and a lack of FDA resources to expedite approval of supplemental new drug applications and conduct

foreign inspections. While not a cause of drug shortages, just-in-time inventory practices by product distributors and practice sites have removed the buffer previously provided by larger inventories and resulted in an immediate impact of drug shortages on patient care.

While information on the root cause of each drug shortage is not always publicly available, the cause of most shortages can be traced back to aspects of the manufacturing process. These manufacturing issues are compounded by substantial industry consolidation over the last few years that has resulted in fewer manufacturers producing critical drugs. When one manufacturer experiences a production interruption, other companies must ramp up production of their product to meet market needs. This increased production is sometimes, but not always, possible. In the case of sole-source drugs, this situation almost instantly results in a shortage situation.

ASHP continues to work with FDA, other health care provider groups and members of the supply chain to address the issue. However, we also believe Congress can help us as well. ASHP supports bipartisan legislation (S. 296, H.R. 2245) that would require drug manufacturers to notify the Agency when they experience an interruption in the production of a drug product potentially resulting in a shortage situation. According to FDA, in 2010 the Agency was able to avoid 38 drug shortages when they were made aware of production interruptions ahead of time. However, we believe other steps can be taken as well, for example, require confidential notification of the disruption in supply of single source active pharmaceutical ingredients (API), require manufacturers to develop continuity of supply plans, establish incentives for manufacturers to remain or re-enter

the market, and urge FDA to develop expedited approval pathways for pre-1938 (unapproved) drugs. Finally, ASHP believes that FDA must have adequate resources devoted to alleviating and preventing drug shortages.

Notification System

Under current law, manufacturers are not required to report to FDA when they experience an interruption in the production of their products, unless that drug is deemed medically necessary by the agency. The same holds true for manufacturer plans to discontinue a product. Even in cases where the drug is deemed medically necessary and reporting is required, FDA has no enforcement mechanism to penalize a drug maker for failing to report these problems. This information could be extremely useful to FDA in the case of drugs with multiple suppliers where the agency could urge alternate suppliers to step up production of a product to offset the decrease in supply due to the interruption or discontinuation of the initial product. In some instances, FDA is not told there is a problem, or the nature of the problem. This information could be useful in determining the duration and severity of the interruption and may allow the agency to implement countermeasures to help ensure supply. By FDA's own account, in 2010 the agency was able to avoid 38 drug shortages when this type of notification was made available.

The importance of notification is highlighted by quality concerns associated with the increased globalization of pharmaceutical manufacturing. A number of drug shortages can be traced back to quality concerns with foreign-produced APIs. An extreme example was

the heparin contamination that occurred in 2007, which resulted in a recall, and subsequent product shortage that was immediate and continued for an extended duration of time. While FDA has increased foreign inspections, it still lacks the resources necessary to fully address this issue. Therefore, drug shortages precipitated by recalls caused by substandard APIs will continue and likely increase.

Legislation (S. 296/H.R. 2245) in Congress would mandate that companies notify FDA of the interruption in production of any product six months in advance, or as soon as possible in the event of an unplanned stoppage. Manufacturers that fail to report this information would be subject to civil monetary penalties. This early warning system would allow the agency to communicate more effectively with manufacturers and others in the supply chain to plan for pending supply interruption. The early warning system should be the cornerstone of congressional action to address drug shortages.

Confidential Notification for Single-Source API

In addition, information that can make drugs vulnerable to shortages, such as a single API source, is also frequently unknown beyond the manufacturer. This information is, and should be considered proprietary, but this lack of transparency hinders the development of contingency plans for vulnerable drugs. A requirement that manufacturers notify FDA when there is a single source of API may help the Agency work with manufacturers to identify backup sources should supply issues arise.

Continuity of Supply Plans

Related to the reporting or an early warning system, FDA could work with manufacturers to develop continuity of supply plans. The current lack of transparency acts as a significant barrier to this type of collaboration. With increased information exchange, contingency plans could be developed that include countermeasures such as manufacturing redundancies or backup supplies; more effective communication among FDA, manufacturers and others in the supply chain; and finally, development of plans that utilize production capabilities of other manufacturers either here in the United States or abroad to ensure availability of a drug in short supply.

In 2010, FDA worked with APP Pharmaceuticals to help alleviate a shortage of propofol, a widely used anesthetic preferred by anesthesiologists because of its excellent safety profile compared to other available drugs. By enabling the company to work with its German counterpart to import the drug, FDA was able to substantially improve product availability after the shortage occurred. Using this example, if an acceptable foreign alternative could be identified before a shortage occurs through establishment of continuity of supply plans for vulnerable drugs, then importation could be expedited and the negative impact of a specific shortage on patient care could be minimized or averted. Importation represents an extreme example of contingency planning. It its simplest form, manufacturing strategies that include collaborating with other manufacturers, establishing back-up suppliers of raw materials and APIs, and creating alternative production capabilities that can be used as countermeasures would be a significant step forward to

combating drug shortages. Contingency planning by companies producing drugs critical to patient care must be a standard of practice. S. 296/H.R. 2245 support the development of contingency plans for drugs that are vulnerable to shortages.

Incentives

Further, shortages are occurring overwhelmingly among generic injectable drugs, where production processes tend to be more complex than their solid dosage counterparts. Low margins for these expired patent products coupled with complex manufacturing processes may lead some manufacturers to abandon production of these drugs altogether in favor of products with higher profit margins, thus reducing the number of potential suppliers of products critical to patient care. A way to offset this problem may be to explore incentives to encourage manufacturers to either stay in the market or enter the market with a new product line. There are several ways this could potentially be accomplished: 1) explore tax incentives for manufacturers to produce a drug in short supply or one deemed "vulnerable" to a shortage; 2) grant temporary exclusivity for a new product line of a drug in shortage or deemed "vulnerable" to one; 3) if a generic user fee program is created within the next reauthorization of the Prescription Drug User Fee Act (PDUFA), FDA could explore reduced user fees for drugs in short supply or deemed "vulnerable."

Require development of an expedited approval pathway for pre-1938 drugs.

FDA must find a way to abbreviate and prioritize approval processes for existing therapies that are unapproved, but widely used and essential for patient care. For these drugs, the agency should work with manufacturers to fast track their approval for the U.S. market, especially in cases where the potential exists for those drugs to fall in short supply. Barriers to manufacturing and marketing these drugs must be minimized in order to foster production and availability of these drugs.

Conclusion

Unfortunately, there is no single solution that can prevent the occurrence of all drug shortages. The complexity of manufacturing processes, the requirement for safe and high-quality products, and globalization of the pharmaceutical supply chain all contribute to fluctuating product supplies that may never be entirely eliminated. However, there are critical steps that Congress, FDA and other stakeholders can implement to ensure that patient care remains available and safe. While the adjustments and compromises required from all stakeholders are difficult, the need for change is critical. First and foremost is the need for increased communication and transparency.

ASHP, along with several other stakeholder groups has been working collaboratively with Congress and supply chain stakeholders to develop solutions to the drug shortage problem. As indicated before, there is legislation in both houses of Congress as well as broad bipartisan support in the Senate for action. Passage of legislation that provides additional authority to FDA is a step in the right direction. In the long term, FDA will

require additional resources to best address this and other issues that impact the quality and safety of drugs.

Mr. PITTS. The chair thanks the gentleman. We are in the middle of votes. We have 14 votes. We are going to try to get a couple more before we go and recess for the vote and we will come back. So Mr. Alkire, you are recognized for 5 minutes.

STATEMENT OF MIKE ALKIRE

Mr. ALKIRE. Thank you. Good morning, Chairman Pitts, Ranking Member Pallone, and members of the committee. I am Mike Alkire, Chief Operating Officer of the Premier Healthcare Alliance. Premier is owned by not-for-profit hospitals and health systems. We use the power of collaboration to lead the transformation to high-quality and cost-effective healthcare. One of the ways we do this is by aggregating the buying power of 2,500 hospitals to get the most effective medical supplies and drugs at the best prices.

I thank the committee for leading efforts to address drug shortages. As you are aware, the number of drug shortages has tripled since 2005 and many of these medicines are essential to patient care. Premier set out to understand the extent of the problem through a survey. We found that between July and December of 2010, more than 240 drugs were either in short supply or completely unavailable in 2010. Over 400 generic equivalents were backordered for more than 5 days. Many of the drugs noted as backordered in 2010 have remained unavailable or in short supply in 2011, and 80 percent of the hospitals reported that shortages resulted in a delay or cancellation of a treatment.

Drug shortages also carry a cost—an estimated $415 million annually through the purchase of more expensive substitutes and additional labor costs. We don't have the ability to estimate the financial impact of shortage drugs where there are no alternatives. We are working to diminish these costs by determining manufacturing capabilities to assess whether a manufacturer can supply the market; we look for alternatives if capabilities don't meet demand; instituting an early warning system for hospitals to notify us of shortages; once notified, we determine the scope of the problem and communicate with the FDA; and exploring longer-term contracts with manufacturers to create more predictable volumes and stability in the market.

In this crisis, we hope people will do everything they can to help patients get the drugs they need. Instead, we have seen the gray market vendors taking advantage of a problem offering to sell shortage products at exorbitant prices. Premier analyzed unsolicited offers from gray market vendors on shortage drugs. We compared their prices to Premier's. We found that average markups were 650 percent and the highest markup was 4,500 percent. In this case, a vial to treat high blood pressure that sells for 25.90 was offered for $1,200. Markups were 4,000 percent for drugs to treat leukemia and non-Hodgkin's lymphoma, 3,100 percent for drugs to help cancer patients to retain bone marrow. Forty-five percent were marked up 1,000 percent above a normal price and a quarter were marked up 2,000 percent.

Where and how gray market vendors are getting these medicines no one knows. And how can the integrity of these drugs be ascertained? Again, a question that few know. That is why Premier has taken a position that pharmacies should avoid these vendors

and stick to known primary distributors. But in times of shortage, pharmacies may need to look elsewhere. In these cases, we develop a set of best practices. These practices include verifying the product's chain of custody, confirming licensure, verifying that a seller is authorized to sell the product, and confirming that the seller is a verified, accredited wholesale distributor.

But in our view, the best way to stop price gouging is to fix the drug shortage crisis. We ask the committee and the FDA to consider the following: speed the approval process for medically necessary drugs that appear to be in shortage; encourage FDA to engage stakeholders in discussions determining whether a drug is medically necessary—the objective is to prioritize drugs that are necessary for treatment and also may be at risk for shortages—grant the DEA flexibility to adjust quotas that are limiting the amount of active ingredients manufacturers may purchase for controlled substances, thus limiting their ability to ramp up production when a supplier exits the market; fast-track approvals of new active pharmaceutical ingredient suppliers for medically necessary drugs in shortage; work with manufacturers to slow the trend of acquiring raw materials outside the U.S.; require manufacturers to notify the FDA of planned supply interruptions—this will allow time to work with remaining manufacturers to increase production—and establish an early warning point of contact at the FDA.

In closing, I thank the committee for the opportunity to share what we have learned about drug shortages and the alarming impact it has on the safety and health of our communities, as well as our healthcare costs. Premier stands ready to assist Congress in finding ways to ensure a safe, reliable drug supply.

[The prepared statement of Mr. Alkire follows:]

TESTIMONY OF MIKE ALKIRE

CHIEF OPERATING OFFICER

PREMIER HEALTHCARE ALLIANCE

ON

Examining the Increase in Drug Shortages

BEFORE THE COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON HEALTH

U.S. HOUSE OF REPRESENTATIVES

September 23, 2011

Good morning Chairman Pitts, Ranking Member Pallone and distinguished Members of the Committee. My name is Mike Alkire and I serve as chief operating officer for the Premier healthcare alliance. I am pleased to be here today on behalf of the more than 2,500 U.S. hospitals and 77,000 other care sites that are members of the Premier healthcare alliance to testify on the pressing issue of our nation's drug shortages. Premier is a performance improvement alliance that is using the power of collaboration to lead the transformation to high quality, cost-effective care. Not-for-profit hospitals created Premier as a way to better serve their patients by overcoming the challenges posed by our fragmented healthcare system. Through the Premier alliance, hospitals, suppliers and the government are united to meet our healthcare system's greatest challenge – advancing quality patient care while controlling costs.

First, I would like to thank you for calling this hearing and for the Committee's strong leadership in addressing the critical problem of shortages in the drug supply. The record shortage of drugs we are currently experiencing has had an adverse effect on the health and safety of communities across the country, and is a contributing factor to rising healthcare costs. Today, I will discuss what several analyses conducted by Premier have revealed about the scope of the shortage problem and its financial and human toll on our nation. I will also offer some initial thoughts about what the Committee, the Food and Drug Administration (FDA) and others can do to address this important issue.

Premier is owned by not-for-profit hospitals, health systems and other providers, and our mission is to improve the health of communities. We operate a leading healthcare purchasing network and maintain the nation's most comprehensive repository of clinical, financial and outcomes information. We are a leader in helping deliver measurable improvements in care and have worked through large-scale hospital collaboratives with organizations including the Centers for Medicare & Medicaid Services to improve hospital performance.

A key component of our alliance is the Premier Pharmacy Program, which combines essential clinical data with purchasing power to deliver reduced costs, improved quality and safety and increased knowledge sharing with other healthcare professionals. Sourcing committees made up of clinical experts from our member hospitals help evaluate current and emerging pharmaceuticals for contracting.

Premier offers a field team of highly qualified pharmacists to help our members enhance their use of medications. Our field experts provide clinically appropriate savings strategies that reduce overall costs and enhance the safe use of medication therapy, analyze high-volume, high-cost drugs and benchmark prescription practices that can help other hospitals improve the performance.

Premier's role in the supply chain is aggregating the buying power of our hospitals to provide the economies of scale necessary to secure the best pricing on drugs for hospitals and other providers. As part of this, we look at appropriate product utilization and comparative effectiveness to help providers get the most effective product at the optimal price. We then negotiate a separate contract with distributors to stock and move the drugs to providers. These are separate contracts, but are both equally important in the supply chain process. Premier monitors to the extent possible how distributors perform in terms of stocking and supplying products and, also to the extent feasible, monitors manufacturers in terms of issues with the FDA, pricing and ability to meet supply demands. Additionally, Premier often acts in a support role for our member facilities, providing guidance on issues of importance to them.

Premier's findings on drug shortages

Our healthcare system has experienced an alarming increase in the number of reported drug shortages for a range of products vital to treatment. More than 45,000 different prescription drug products are on the market today, originating from about 1,400 different manufacturers. Each year, the U.S. experiences a shortage of some number of these products, but the frequency and

impact of drug shortages has risen to critical levels, more than tripling since 2005 and affecting all segments of healthcare. According to the University of Utah's Drug Information Service, the current list of shortages is already the longest in a decade at 180 products. Shortages are getting so severe that it is expected that more than 211 products will be unavailable by the end of the year. Many of these medicines are essential to patient care, and include those used in chemotherapy, sedation to conduct surgeries and emergency treatments for heart attack patients.

Faced with these escalating shortages, Premier set out to better understand the extent of shortages, how they are impacting our hospitals and other care sites' ability to access the drugs needed for patient care, and to identify potential strategies to mitigate the problem. In March, Premier conducted a survey of 311 pharmacy experts representing 228 hospitals, as well as infusion, oncology and surgery centers, outpatient and retail pharmacies and long-term care facilities. The survey revealed that over the course of a six-month period (July-December 2010):

- More than 240 drugs were either in short supply or completely unavailable in 2010.
- Over 400 generic equivalents were back-ordered for more than five days.
- Many of the drugs noted as back orders in 2010 have remained unavailable or in short supply in 2011.
- This represents a dramatic increase in drug shortages over the last five years.

The American Hospital Association (AHA) also conducted a recent survey that affirms Premier's findings. The AHA survey showed that 99.5 percent of hospitals reported experiencing one or

more drug shortage in the last six months, and nearly half of the hospitals reported 21 or more drug shortages.

Impact on patient care

A shortage in the supply of a prescription drug can have serious implications for patient care. In the hospital setting, a shortage may result in the delay of medical procedures. Substitution of therapeutic or similar medications, if available, may lead to medication errors and preventable adverse events especially when prescribers are not as familiar with the alternative products' dosing and potential for adverse interactions with other drugs. Some second or third choice products also may be less clinically effective. And in some cases, concerns arise about the reliability of the source of the drugs, which may be outside the U.S., and whether they have been properly handled throughout the chain of custody.

In evaluating the threat of drug shortages to patient safety, Premier's survey found:

- 89 percent of hospitals experienced shortages that had the potential to cause a medication safety issue or an error in patient care, and 53 percent suggested this occurred more than six times. We see this, for example, when drugs are not available and therefore cannot be used to treat the patient's condition, or when a physician has to use a drug as a substitute that has a different dosing parameter that is unfamiliar in the clinical setting.

- 80 percent of hospitals experienced shortages that resulted in a delay or cancellation of a patient care intervention, and 34 percent suggested this occurred more than six times.

Examples of these incidences include chemotherapy delays or cancelations due to unavailable oncology drugs and delays in surgery due to lack of anesthesia agents.

Financial impact of drug shortages

The growing problem of drug shortages is also extremely costly to hospitals and to the healthcare system as a whole. Premier's survey found that 98 percent of hospitals experienced shortages that resulted in an increase in costs; 88 percent suggested this occurred more than six times; and 41 percent suggested this occurred more than 21 times. Steps needed to respond to shortages can divert important resources away from improving care. The cost in time and money can be especially high when hospitals and other providers face shortages in drugs that are needed to respond to new treatment guidelines and to treat victims of natural and other catastrophes where disease outbreaks, for example, threaten large numbers of people.

Premier's ability to analyze the expansive pharmaceutical supply chain data of our members has enabled us to provide financial impact snapshots of drug shortages. Combined with results from other organizations' analyses on drug shortages, these findings suggest that **shortages could cost U.S. hospitals at least $415 million annually** through the purchase of more expensive generic or therapeutic substitutes and additional labor costs.

- According to Premier's analysis, the annual financial impact of drug shortages on *Premier alliance members alone* where generic alternatives are available exceeds **$78 million**. More than $66 million (or 85 percent) of the impact is felt by Premier's 2,500 hospital members, with the remaining amount within Premier's non-acute care sites. The highest areas of cost

are infectious disease ($22.5 million), surgery ($12 million), oncology ($10.5 million), and cardiovascular therapies ($8.5 million).

- Extrapolating nationwide from the analysis findings, Premier found drug shortages cost *all U.S. hospitals* at least $200 million annually through the purchase of more expensive generic or therapeutic substitutes. This is a conservative estimate and excludes drugs purchased on the "gray market," or with therapeutic alternatives. Premier conducted a separate analysis on the dramatic impact on pricing that the gray market has, which I will review later in my testimony. Our research also does not include indirect costs such as added labor needed to manage shortages and secure alternative supplies.

- A survey conducted by the American Society of Health-System Pharmacists and the University of Michigan Health System addressed this area and found that the labor costs and time required to manage shortages translates to an estimated annual impact of $216 million nationally.

Premier's gray market analysis

We might hope that in this time of crisis, people would band together and do everything they could to help patients get the drugs they need, when they need them. Rather, we have seen numerous "gray market" vendors taking advantage of the shortage situation, attempting to sell shortage products at exorbitant prices to enrich themselves. These vendors are attempting to

capitalize on the desperation of pharmacy directors and buyers who are finding it increasingly difficult to secure a sufficient supply of the drugs needed to meet all of their patient care needs.

The gray market, also known as a parallel market, is a supply channel that is unofficial, unauthorized or unintended by the original manufacturer. In markets where the products are scarce or in short supply, gray markets evolve to sell the item at any price the market will bear.

Over the last year, Premier has received many requests from our alliance member hospitals, asking for assistance with the growing trend of price gouging efforts by these gray market vendors and understanding the pedigree of a drug purchased from the gray market. In response, Premier developed a series of recommendations to help our members and providers nationwide avoid gray market vendors and identify safe buying opportunities. I will touch on these recommendations further in a few moments.

Along with the recommendations, we also did some research on this situation. Over a two-month period, Premier members turned over 1,745 unsolicited sales offers from gray market vendors. The offers came in the form of marketing emails and fliers. All offered to sell shortage drugs, and sometimes excluded price or the code needed to properly identify and track the drug. Of these offers, the 636 that contained both the price and the proper drug identification number were analyzed and compared to Premier's standard contracted prices for these medicines.

The results were appalling.

The average markup being offered to hospitals by these gray market vendors is 650 percent, and many others were far higher. In fact, **the highest markup was more than 4,500 percent.** In this case a drug used to treat high blood pressure, which normally sells for $25.90, was being offered at $1,200 – a staggering increase. Forty-five percent of the offers were marked up at least 1,000 percent above normal price. And, over a quarter of them were marked up at least 2,000 percent above normal price.

In other cases, offered markups were as high as 4,000 percent for chemotherapy medicines to treat leukemia and non-Hodgkin's lymphoma and 3,100 percent for medicines to help cancer patients retain bone marrow. We saw similar markups for medicines for sedation during surgeries; to dilate veins and prevent brain or heart spasms; and to prevent damage during a heart attack.

Considering the nation's budget crisis and our skyrocketing healthcare bill, these markups are nothing more than profiteering at the expense of patients and providers who are struggling to afford vital medicines needed for patient care. Price gouging in healthcare is so troubling to us because it is taking advantage of some of our most vulnerable citizens: the grandmothers who need chemotherapy to survive; the father who goes to the hospital for a heart attack; and the children suffering from leukemia.

Safety concerns with the gray market

Not only are pharmacies and patients being asked to pay the price gouger's premium, but in some cases, they cannot be sure that the medication is safe or even authentic. When price

gougers emerge with products, it begs several questions. Where and how are they getting medicines that no one else can? And how can the integrity of these drugs be ascertained?

When a gray market vendor enters the market, it is not unheard of for a drug to be bought and sold four or five times in the same day. You can imagine if a product changes hands that many times, the price is going to increase with each sales transaction.

Premier's response to the drug shortage situation

As I mentioned, members of Premier have asked us to help them cope with the drug shortage situation and, in particular, help them ensure safe purchases.

Premier believes that new measures and accelerated efforts are needed to address situations with prescription drug shortages and is helping members navigate the ongoing situation. We are working aggressively to diminish shortage-related costs to member hospitals. Our expansive supply chain data repository provides unique opportunities to source drugs from suppliers that demonstrate the ability to safely meet member market demands.

Specifically, Premier is:

- **Working with manufacturers:** We are working closely with manufacturers to determine their manufacturing capabilities at the front end when contracting to determine if they can

supply the market. Premier looks for alternatives if manufacturer's capabilities cannot meet demand.

- **Maintaining a hospital communication network:** Premier has instituted an early warning system in which hospitals notify Premier of drug access problems, even before they are posted on the FDA website. Once notified of a drug shortage, we determine if it is a local or national problem and regularly communicate this information to the FDA to make them aware of what is being shorted. Premier provides guidelines to hospitals on what steps to take to help reduce financial and quality impact of drug shortages. And, in collaboration with our members, we have developed toolkits, programs and professional advisories to help members manage drug shortages.

- **Creating longer term contracts:** Premier is seeking contracts that are longer in duration to enhance a stable market.

Premier has taken a firm position that hospital pharmacies should avoid the gray market, and stick to purchasing from known organizations. To help our members and providers nationwide source safe and effective drugs, Premier pharmacy staff developed recommendations, including the following best practices that should be followed whenever purchases are made outside a hospital's known, established primary distributor:

- Ask for and confirm receipt of a drug pedigree that records the products' chain of custody.

- Confirm with State Board of Pharmacy or Department of Health that the seller is appropriately licensed and not subject to any current investigations.

- Verify with the product manufacturer that the distributor is an authorized distributor of record (ADR).

- Keep records of sellers you have refused to do business with and reasons why, and confirm the distributor is a Verified-Accredited Wholesale Distributor (VAWD) through the National Boards of Pharmacy. VAWD ensures a higher level of assurance due to this accreditation.

Though these recommendations are intended to protect our members and the patients they serve from unintended harm, even if they are followed, they do not guarantee that all selected sellers will be legitimate. We do, however, feel strongly that they will help.

Recommendations to address the drug shortage crisis

Lastly, I would like to suggest some ideas to address the drug shortage crisis. While the Premier healthcare alliance is employing the measures I described to ensure better preparation for a drug shortage and processes to deal with it, private sector initiatives can only go so far in addressing the problem.

We ask the Committee and the FDA to consider:

- Shortening the approval process for medically necessary generic drugs that appear to be in shortage.

- Encouraging the FDA Drug Shortage Program staff to broadly engage members of the healthcare community in discussions determining whether a drug is "medically necessary. The objective here is to assist with prioritizing which drugs are critically necessary for treatment and may also be at risk for drug shortage due to insufficient manufacturing capacity. A first step in this effort could be creating a workgroup to guide FDA's decisions on designating a drug as medically necessary.

- Enabling more flexibility in regulations that apply to quotas to registered manufacturers of controlled substances. The Drug Enforcement Agency (DEA) currently limits the amount of active ingredients manufacturers may purchase for controlled substances, thus limiting the ability of manufacturers to ramp up production when another supplier exits the market. Flexibility should be afforded to allow the DEA to expeditiously modify or transfer these quotas among manufacturers when one ceases production of a drug containing a controlled substance.

- Creating a fast track approval of new Active Pharmaceutical Ingredient (API) suppliers for medically necessary drugs in shortage.

- Working with manufacturers to slow the trend of acquiring the bulk of the raw materials used in pharmaceuticals outside of the U.S. For raw materials overseas, the manufacturers should be required to inspect the facility from which they are purchasing.

- Requiring manufacturers to provide the FDA notification of planned discontinuation or interruption in the manufacture of drugs as soon as practicable after determining the current production will not meet average historic demand. This will allow FDA time to work with remaining manufacturers to increase production.

- Creating a stakeholder committee to advise FDA on market conditions.

Premier will continue to look at the data on drug shortages and talk to our hospital members, manufactures and others to identify potential solutions. To this end, Premier is a member of a multi-stakeholder workgroup that emerged from last year's FDA/stakeholder summit to seek solutions.

In closing, I would again like to thank the Committee for the opportunity to share what we have learned about the scope of drug shortages and the alarming impact it has on the safety and health of our communities, as well as its part in driving up healthcare costs. The Premier healthcare alliance appreciates the Committee's recognition of the urgency in which this problem needs to be addressed, and we stand ready to help Congress find achievable ways to ensure a safe, reliable drug supply.

Mr. PITTS. The chair thanks the gentleman. And again, we appreciate your patience. We have got 5 minutes left for a vote. I think we will break here and come back as soon as the last vote is over and continue the testimony.

The chair recognizes Mr. Pallone.

Mr. PALLONE. Mr. Chairman, I just wanted to ask unanimous consent to submit the written statement for the record of Congressman Matheson.

Mr. PITTS. Without objection, so ordered.

At this point, the subcommittee stands in recess until after the last vote.

[Recess.]

Mr. PITTS. The subcommittee will come to order. Again, I apologize for the schedule, and I appreciate very much your patience and your thoughtful testimony. We will resume the testimony with Dr. Penley. I believe you are up next, so you have 5 minutes.

STATEMENT OF W. CHARLES PENLEY

Mr. PENLEY. Good afternoon, Chairman Pitts, Ranking Member Pallone, and the remainder of the subcommittee. I am Charlie Penley, and I am a practicing oncologist in Nashville, Tennessee. I spend the majority of my time taking care of patients, and this is why I am pretty uncomfortable in this environment. But I am here today to talk about the impact of drug shortages on my patients. I speak today on behalf of the American Society of Clinical Oncology. Our 30,000 members and their patients thank you for holding this hearing. Drug shortages have indeed reached crisis proportions in oncology. We hope that this hearing will better frame potential solutions.

ASCO is hearing from practices all around the country, large and small, community-based and hospital-based practices who are having challenges treating their patients. The situation, as you have heard this morning, is worsening. Drug shortages in the United States have tripled since 2005/2006. Almost all cancer types are affected—leukemia, lymphoma, breast cancer, ovarian cancer, testicular cancer, and colon cancer. Shortages are indeed forcing us to change the way we treat our patients. Often, a drug in short supply is potentially curative. There is no reasonable substitute.

Our practice treats many patients who have been diagnosed with acute myelogenous leukemia, AML. It is a life-threatening but potentially curable disease. Cytarabine, as you have heard, is one of the essential components of treatment for AML but that agent has been and remains intermittently in short supply today. Physicians have been forced to tell patients that this potentially curative drug is not immediately available to them. Treatment delay can result in grave consequences in these critically ill patients.

In other situations, there are alternative drugs, but they are less effective, they have more side effects, or they are dramatically more expensive. For example, the standard treatment for non-Hodgkin's lymphoma is known as the CHOP regimen. CHOP chemotherapy includes doxorubicin, which has been and is in shortage. A colleague shared the story of a young woman who was recently diagnosed with lymphoma during pregnancy. Now, that is a very complex situation which fortunately doesn't happen very often, but it

involves potential risks for both the mother and the child. Because of the doxorubicin shortage, the woman had to be treated with a substitute, one for which the risk for the baby is not as well known and which may be less effective treatment for her lymphoma. Oncologists and patients should not have to make such difficult choices.

I am currently treating a national firefighter who has an advanced gastrointestinal cancer and who was responding to 5–FU based chemotherapy. Earlier this summer, we were unable to obtain 5–FU and had to use an alternative regimen, which both caused him more personal side effects and significantly increased his out-of-pocket cost.

The price of substitute drugs can be up to 100 times more expensive than the drug normally chosen, especially if the substitute is a brand name drug. As an example, when the mainstay generic drug leucovorin went into shortage, oncologists had to treat patients with the substitute, levoleucovorin. Medicare payment for 50 milligrams of leucovorin is $1.25. An equivalent dose of levoleucovorin is approximately $90.

The clinical trials infrastructure in this country is threatened by drug shortages as researchers alter or delay trials because the drug that is part of the study becomes unavailable. As many as 60 percent of clinical trials have been delayed, this at a time of great promise in cancer research.

We understand that there are many causes of this problem, a number of them involving the manufacturing process. However, market factors appear to be a key driver in this rapidly escalating crisis. Shortages in cancer drugs are almost exclusively in generic sterile injectables, which are generally inexpensive drugs with a very low profit margin. Companies that experience manufacturing complications may not have the incentives to invest resources required to upgrade facilities or to correct quality problems.

As we have heard, there does not appear to be a single solution to the crisis. Our primary expertise is in patient care, but we would offer these potential solutions, which we would encourage the committee to explore. First, Congress should urge expedited abbreviated new drug applications, or ANDAs, for drugs vulnerable to shortage in a way that does not compromise safety. Secondly, because this amounts to a public health crisis, Congress could work with Medicare to address pricing and payment for ultra-low-cost generic drugs. Third, Congress should pass S. 296 and H.R. 2245, bipartisan legislation that would give the FDA increased authority to manage the shortages. Fourth, consider tax incentives to encourage or enable generic manufacturers to continue to produce vital drugs, update their facilities, or enter the market to produce the drugs vulnerable to shortage.

Mr. Chairman, ASCO has been and will remain an active partner in seeking resolution to the problem. The stress of dealing with a cancer diagnosis and the risks of necessary treatment is a heavy enough burden for patients and families to bear. It is absolutely unacceptable that the lack of effective oncologic therapeutics should add to that stress, or worse, threaten lives. We must do everything in our power to resolve this crisis, and we should do it imme-

diately. We appreciate your leadership on this issue, and we stand ready to do everything that we can to assist. Thank you very much.

[The prepared statement of Mr. Penley follows:]

Testimony of W. Charles Penley, MD

On behalf of

The American Society of Clinical Oncology

Before the

Subcommittee on Health of the Committee on Energy and Commerce

Hearing Examining the Increase in Drug Shortages

September 23, 2011

Thank you for the opportunity to submit testimony before the Subcommittee on Health of the Energy and Commerce Committee on the issue of drug shortages. My name is Charles Penley. I am a practicing oncologist in Nashville, Tennessee. I serve as incoming Chair of the Government Relations Committee of the American Society of Clinical Oncology (ASCO), am a past Chair of the Clinical Practice Committee, and currently serve on the Board of Directors of the Conquer Cancer Foundation of ASCO. I spend the majority of my time engaged in direct patient care, and am here to today to talk about the impact of drug shortages on my patients and my practice. I will also address what ASCO perceives to be the many causes contributing to shortages and suggest potential avenues Congress could take to alleviate this growing crisis.

ASCO is the leading specialty society in the United States and throughout the world for physicians who treat people with cancer and conduct oncology research that leads to improved patient outcomes. On behalf of our 30,000 members and the patients that we serve, I wish to thank this committee for shining a light on this difficult situation which impacts oncologists and their patients. ASCO is committed to ensuring that high quality, evidence-based practices for the prevention, diagnosis and treatment of cancer are available to all Americans in every community throughout the United States. This goal is impossible to achieve when many critical, and often curative, anti-cancer agents are not available. Sadly, that is the reality we face today.

My testimony will touch on the following points:

- The dire consequences for patient care when a critical cancer drug is in short supply;
- The many and diverse causes of the drug shortages;

- The need for both legislative and regulatory action to reduce drug shortages in oncology; and
- Potential solutions that may warrant further exploration.

Shortages of critical drugs used to treat and cure cancer are increasing daily, forcing changes in treatment to less effective therapies, delays in treatment, increased costs to patients and potential denial of curative therapy. In some situations, the drug in short supply is curative, and no meaningful clinical option exists. In other situations, an alternative exists, but is less desirable for one or more of the following reasons: a) we know with certainty or have strong reason to believe that the likelihood of cure is significantly diminished using the alternative drug; b) we may know that the side effects or quality of life are significantly worse under the alternative drugs; c) we may lack the scientific evidence to know whether the alternative drug is equally effective; and d) the alternative drug may be dramatically more expensive, increasing patient co-pays and the cost to the system.

Some examples from my practice in Nashville are illustrative of how these difficult situations play out with patients. Our practice treats a number of people each year who have been diagnosed with acute myelogenous leukemia (AML). For many patients, AML is a potentially curable disease. Cytarabine (Ara-C) is an essential component of treatment for AML, but this drug is in short supply today. There is simply no substitute, leaving many of our physicians in the situation of telling patients that this potentially curative therapy is not available to them. In these situations, treatment delays can result in poorer outcomes.

Some drugs in shortage have substitutes, but there is often less data available to support their use. For example, daunorubicin and doxorubicin—both used in the treatment of several common cancers – have been in short supply for months. The standard of care for patients with intermediate grade non-Hodgkin's lymphoma, a curable malignancy, is the CHOP regimen, which includes doxorubicin. This regimen has been in use since the 1970's and remains the gold standard today. Deviation from this standard has in the past been shown to lead to poorer outcomes for patients. A colleague of mine has shared the story of a young pregnant woman who was also recently diagnosed with lymphoma. The same CHOP regimen, which is curative for the mother, can be given safely in pregnancy with acceptable risk to the baby. Because this regimen is not available, my colleague had to treat her with a substitute therapy where the data are less clear about her outcome and the effect on the baby. As you can see, while there may be available substitutions for doxorubicin and other drugs used to treat lymphoma, the choice we are forced to make is to use a workaround that include inferior agents with less certain clinical effect. Oncologists and patients should not have to make such a choice.

Beyond the unacceptable fact that patients are not receiving "standard of care" treatment in the richest country in the world, the situation is causing emotional and economic hardship for cancer patients. One of my patients, a Nashville firefighter, has advanced gastrointestinal cancer. He was responding to 5-FU based combination chemotherapy. 5-FU is a commonly used and effective drug, one that has been in the chemotherapy arsenal for many years. Earlier this summer our practice was unable to obtain 5-FU, and we were forced to change to another

chemotherapy regimen. My patient has endured increased out of pocket costs and additional side effects as a result of this alternative treatment.

It is no exaggeration to say that the price of substitute drugs can be 100 times more than the drug you would normally use—and that does not factor in the gray market that has emerged in response to these ongoing shortages. In cases where the workaround involves substituting a brand name drug for a generic, out of pocket expenses for patients and cost to the Medicare program are greatly increased. For example, when the mainstay generic drug leucovorin went into shortage, oncologists had to treat patients with the appropriate clinical substitute, levo-leucovorin, which is a different formulation of leucovorin, available as a brand name only. The price differential for the Medicare program is significant - for 50mg of leucovorin the Medicare payment is approximately $1.25, compared to 50mg of levo-leucovorin which is approximately $180. Beyond the costs to the patients and the Medicare program, practices are having to divert precious resources, in an already difficult economic environment, to hire full time staff whose job is to locate drugs in shortage, so patients may receive treatment.

My practice and our patients are not alone in facing these problems. ASCO is hearing from practices all around the country – small and large, community and hospital based – that are encountering the same challenges treating their patients. In fact, according to the University of Utah Drug Information Service which tracks this information, U.S. drug shortages have tripled since 2006 and we are currently on a path that will end 2011 with over 300 drugs in shortage in the United States. Cancer drugs are particularly vulnerable to shortage because many of them

are in the form of sterile injectables, which made up approximately 70% of shortages in 2010. This crisis is not discriminating by disease - ASCO is seeing shortages across the spectrum of cancer including leukemia, lymphoma, breast, ovarian, testicular, and colon cancer.

The clinical trials infrastructure in this country is also threatened by drug shortages. Researchers have had to alter or delay trials when a drug that is part of the study becomes unavailable. Over 150 NCI-sponsored trials include drugs that are currently in shortage. We have heard from at least one NCI Cooperative Group that patient accrual in 60% of trials has been delayed due to drug shortages. Beyond affecting immediate patient care, this crisis is stalling progress at a time of great promise in cancer research.

There appear to be many factors contributing to drug shortages in oncology. In November of 2010, after hearing from our members about increasing shortages of oncology drugs, ASCO joined with other affected stakeholder groups in convening a summit to address the scope and causes of the issue. Based on that forum and many subsequent interactions across the medical community, the complexity of this crisis has become apparent. We learned there are many reasons a sterile injectable drugs can be in short supply. Manufacturers report problems with supply of raw materials or the unavailability of active pharmaceutical ingredients (API), manufacturing stoppages due to product quality issues, and other manufacturing difficulties as some of the main causes of drug shortages. Product discontinuations or market shifts due to consolidation are also contributing factors. At the same time, economic constraints have

caused distributors and practices to institute "just in time" inventory models allowing for less product to remain in stock resulting in a more immediate effect when a drug enters a shortage.

Apart from manufacturing issues, it has become abundantly clear that market factors are playing a substantial role in this rapidly escalating crisis. Shortages in cancer drugs are almost exclusively in generic sterile injectables, which are generally inexpensive drugs with a very low profit margin. Companies that experience raw material or other manufacturing complications do not have the incentive to invest resources required to upgrade facilities or correct quality problems; it is not a good business decision. Further, regulatory compliance and administrative costs of resuming production—or of another company stepping in--may tip the cost benefit analysis toward discontinuing production of these agents.

Legislative or regulatory action should play a role in streamlining administrative barriers and encouraging manufacturing of generic pharmaceuticals in order to address shortages.
There is no single solution that will address the myriad problems in a complex manufacturing and distribution system. However, there may be several strategies that, used in concert, could begin to make a difference. ASCO's primary expertise is in the clinical management of this crisis, but we share the following ideas in the interest of advancing the discussion toward finding solutions. We urge the Committee to explore these and other options with relevant stakeholders.

- Regulatory Action: Quicker approval or removal of administrative barriers may encourage new manufacturers to enter the generic market, or encourage current manufacturers to remain in the market. One mechanism should be to expedite Abbreviated New Drug Applications (ANDAs) for drugs vulnerable to shortage in a way that does not compromise drug quality or patient safety. The process for ANDA approval may take up to two and a half years – for drugs in shortage that should and could be reduced to a few months. We are aware that FDA is working to expedite applications for drugs in shortage, but the Congress should ensure that the FDA has adequate resources to handle any increased capacity necessary to mitigate shortages.

- Address updates to generic drug prices: This might include reconsideration of the methodology used by Medicare to establish and update payment levels for ultra-low cost generic drugs. When Congress established the average sales price (ASP) methodology for drugs under Medicare Part B, it included an exception to the standard ASP methodology for instances in which a public health emergency arises. Using a similar approach, Congress could consider creating reimbursement safeguards under Medicare Part B as a way to promote production of ultra-low cost generic drugs that are vulnerable or approaching shortage.

Apart from this step, Medicare could speed reporting and updates of the average sales price (ASP) for drugs paid under Part B of the Medicare system, including generic sterile injectables. Current policy results in a six-month lag between reporting by manufacturers to the Centers for Medicare & Medicaid Services (CMS) and the subsequent update of Medicare reimbursement rates. Existing technology should allow CMS to update sales prices for generic drugs in real time, which would help to more accurately reflect shifting market dynamics.

- Increased Notification: ASCO supports bipartisan legislation introduced in both the House and the Senate that would give the Food and Drug Administration (FDA) increased authority to manage shortages. S. 296 and H.R. 2245 would authorize the FDA to mandate notification by manufacturers when they become aware of potential supply disruptions. This legislation includes confidentiality provisions to avoid inciting hoarding to the extent practicable. It may be impossible to safeguard against hoarding altogether, as it is clear that hoarding is occurring under the current system. We know from the FDA that it was able to prevent 38 shortages last year because it had early warning of problems at the manufacturer level. We understand increased notification is not sufficient to solve the crisis in the absence of other significant steps, but early notification can only help to ease the drug shortages crisis.

- Tax rebates or tax credits: Tax incentives may encourage or enable generic manufacturers to continue to produce the drugs and update their facilities, or enter the market to produce drugs vulnerable to a shortage. Any incentive should be structured in a way to allow for multiple manufacturers to enter and stay in the market to guard against a shortage caused by quality issues experienced by a sole source manufacturer.

  Tax incentives could be considered for companies that do one or more of the following: invest in infrastructure to allow sufficient excess inventory of drugs; establish robust continuity of production plans (e.g. a manufacturer that keeps extra production lines "clean" and ready to start at short notice); commit to produce drugs vulnerable to shortage for a specified uninterrupted period of time; re-enter the market or increase production when a drug goes on shortage.

- Other governmental action: Previously established governmental programs could prove instructive. There is precedence for government intervention in situations when public health is threatened, as was the case with vaccines. Additionally, consideration should also be given to increasing collaboration between government agencies to achieve a stockpiling program similar to that used in counter terrorism.

Mr. Chairman, ASCO has been—and will remain—an active participant in seeking resolution to this problem. The most difficult thing in the world is to sit across from a patient who has the

potential for a cure—and tell them we do not have the necessary therapeutic agents. Oncologists and their patients face incredibly difficult decisions on a daily basis. The stress of dealing with a cancer diagnosis and the necessary treatment is a heavy burden for patients and families to bear. It is absolutely unacceptable that the lack of effective oncologic therapeutics should add to that stress or worse, threaten lives. We must do everything in our power to resolve this crisis, and we should do it immediately. We appreciate your leadership on this issue and stand ready to do everything we can to assist.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Lancaster, Mr. Paoletti.

STATEMENT OF RICHARD D. PAOLETTI

Mr. PAOLETTI. Good afternoon. I want to thank the committee for convening this hearing and for the opportunity to participate in this important discussion. My name is Rich Paoletti, and I am vice president of operations at Lancaster General Health in Lancaster, Pennsylvania. My comments today will address the daily challenges hospitals, patients, and providers are experiencing as a result of increasing drug shortages occurring nationwide.

In the current healthcare climate, hospitals are being asked to restructure to meet the quality, safety, fiscal constraint, and community-benefit standards expected in today's world. Our resources are being stretched to the limit. Ongoing drug shortage challenges at Lancaster General are further taxing and diverting those resources to respond to the almost-daily patient impacts these shortages create. This pattern is increasingly becoming the norm for hospitals, physician practices, emergency responders, and most importantly, patients everywhere.

At Lancaster General, we work hard to maintain a culture of quality and patient safety largely based on fundamental building blocks of standardization through elimination of waste and variability. In direct conflict with these safety practices, drug shortages add variability, complexity, and additional burden, increasing the possibility of medication misadventure, poor outcomes, and patient harm.

The lack of an early warning system regarding impending shortages is one of the greatest challenges we face as healthcare providers, such that sometimes learn about shortages or their severity when products are not received in our daily shipments.

A review of our drug wholesaler orders last month revealed receipt of only 3,452 of the 4,344 line items orders processed, representing a fill-rate of about 80 percent. In other words, 892 line items ordered in August were not received. Every disruption to medication supply creates new responsibilities to investigate alternative treatments and evidence to update protocols, procedures, and various technologies. Additionally, we must disseminate effective education on alternatives not always readily familiar to frontline caregivers. In our fast-paced, complex environment, every substitution adds variation and risk.

These logistical tasks consume significant dedicated hours from multiple stakeholders and staff working collaboratively on detailed plans to maintain safety, while requiring execution in limited timeframes. This means working with anesthesiologists and emergency physicians in contemplating how we might maintain airway in a patient presenting to the trauma center without the availability of a paralyzing agent; neonatologists considering how we may best provide nutritional care to compromised premature infants; infectious disease specialists searching for alternative anti-infectives; and oncologists discussing alternative treatment regimens midway through a course of therapy; and more importantly, how we will reveal to patients that we may not have the medication necessary to

treat their ailments. In our opinion, this issue represents the national healthcare crisis.

Relieving and minimizing avoidable drug shortages requires both short-term interventions and longer-term, permanent solutions. These potential solutions require system changes and increased capacity, including the following: establish an early warning system as proposed in bipartisan legislation currently in both Houses of Congress to immediately help to avert or mitigate drug shortages proactively; establish and improve communications between the FDA and manufacturers to develop evidence-based allocation plans for critical drug therapies; secure the pharmaceutical supply chain; and direct available supplies to our most critical patient populations; explore incentives to encourage drug manufacturers to stay in, reenter, or initially enter the market critical to specific drugs in short supply. These could include creation of a fast-track for approval of new production lines, alternative manufacturing sites, or new suppliers of raw materials for medically necessary drugs in shortage or vulnerable to shortage without compromising the quality and safety.

Again, I want to thank the committee for holding this hearing. Lancaster General Health offers its continued support and commitment to assist in the development of solutions that will help to prevent and mitigate risks caused by drug shortages. Thank you.

[The prepared statement of Mr. Paoletti follows:]

Statement of

Richard D. Paoletti, MBA, RPh, FASHP
Vice President, Operations- Pharmacy, Laboratory, and Radiology
Lancaster General Health

Before the
United States House of Representatives Committee on Energy and Commerce
Health Sub-Committee

"Examining The Increase In Drug Shortages"

Friday, September 23, 2011, 9:30 am

Introduction

Good morning and thank you for the opportunity to participate in this hearing today. My name is Rich Paoletti and I am a pharmacist and Vice President of Operations at Lancaster General Health in Lancaster, PA. My comments today will address the daily challenges hospitals, patients, and providers are experiencing as a result of the increasing drug shortages occurring nationwide. On behalf of Lancaster General Health, I applaud the Committee for holding this hearing.

Background

Lancaster General Health is an acute care community hospital and level II trauma center with over 600 beds and 7000 employees, located in a county with a population just over 500,000. With a current annual drug budget of approximately $43.5 million, our institution dispenses an estimated 12,000 doses of medication per day and receives daily shipments of medications six days per week. Although our organization has always focused on quality and safety, the IOM Report "To Err is Human," was a catalyst for an improved focus on a culture of safety developed over the past decade. The fundamental building blocks to this culture are largely based on standardization and elimination of waste and variability. The requirement for safe, secure, and efficient medication management in our institution relies heavily on intelligent leveraging of automation and technology including, but not limited to, electronic order management software, automated storage and retrieval systems, decentralized dispensing cabinets, barcode-medication administration, and intelligent infusion devices.

In the current healthcare climate, hospitals are being asked to re-structure to meet the quality, safety, fiscal constraint, and community benefit standards expected in today's world. Our resources are being stretched to the limit. At the same time, the number of documented drug shortages has nearly quadrupled in the United States over the past five years and presently, there are at least 198 drug shortages[1,2], spanning multiple therapeutic classes, ranging from nutritional supplements to chemotherapy agents and many other categories in between.

Ongoing drug shortage challenges at Lancaster General Health are increasingly becoming the norm and are resonating across hospitals, physician practices, emergency responders - and most importantly – patients every day. At Lancaster General Health, we strive to maintain a culture of quality and patient safety largely based on the fundamental building blocks of standardization through elimination of waste and variability. In direct conflict with

these safety practices, drug shortages add variability, complexity and additional burden, increasing the possibility of medication misadventure, poor outcomes and patient harm.

The lack of an early warning system regarding impending shortages is one of the greatest challenges we face as healthcare providers, such that we sometimes learn about shortages or their severity when products are not received in our daily shipments.

A review of our drug wholesaler ordering patterns last month (August 2011) demonstrated a 79.5% raw service level; of 4,344 line items ordered, only 3,452 were supplied; 892 line items were not available and, of those 892, only 25 were temporary issues within the control of the wholesaler.

Aug-11	Lines Ordered	Wholesaler Out	All Other Exception Lines	Lines Filled	Raw Service Level %
ACCT 1	3292	19	572	2701	82.05%
ACCT 2	731	4	280	447	61.15%
ACCT 3	321	2	15	304	94.70%
TOTAL	4344	25	867	3452	79.47%

Every disruption to medication supply creates new responsibilities to investigate alternative treatments and evidence, and to update protocols, procedures, and various technologies. Additionally, the hospital must disseminate effective education on alternatives not always readily familiar to frontline caregivers. In our fast-paced, complex environment, every substitution adds variation and risk.

Manufacturer consolidations, in some cases, have exacerbated this problem by reducing the number of facilities that produce critical drugs to one or two sources worldwide. As a result, even a small shift in a facility's production lines can eliminate the availability of drugs for days. Hospitals are also unable to buffer the impact of drug shortages due to the need for just-in-time inventory controls that are necessary in today's fiscal environment.

Some examples of how these decisions and realities impact patients include the following:

Causes:

- Increased demand for a product (can be due to sole source suppliers, other manufacturers exiting the market on a particular product)
- Natural disasters
- Raw materials shortages
- Manufacturing / Regulatory issues
- Recalls
- Changes in licensing and/or changes in formulation

Challenges

- The lack of an advance warning system (often, hospital staff are only able to detect a shortage when they receive fewer units than expected from a wholesale order)
- Communications by manufacturer and FDA often lag behind the discovery of shortages at the point of care
- Current FDA authority is inadequate to ensure a consistent supply of medications
- Institutions must stretch their resources in order to adequately manage shortages

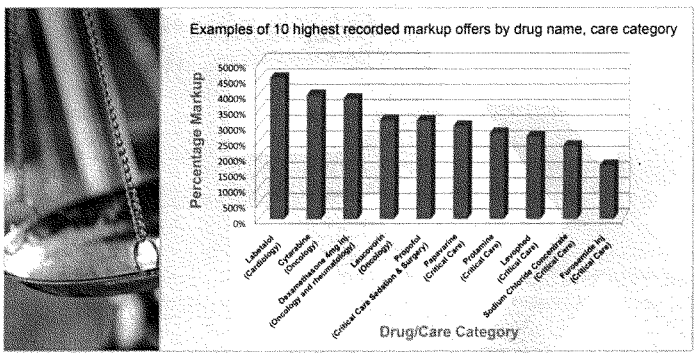
Impact

Financial

Drug shortages can have a significant financial impact on hospitals by affecting market prices and adding administrative costs in order to adapt to shortages. The enormous amount of time required to mitigate drug shortages also takes hard-working employees away from patient-centered activities. Healthcare organizations, as a result of this time-consuming activity, must bear additional administrative and wage costs, as well.

For example, when a shortage of a niche product arises, the price of that product can rise rapidly upon reintroduction into the market. This type of shortage can occur when pharmaceutical companies sell the rights to these products to smaller firms. When the new owners of the drug reintroduce it to the market, acquisition costs can sometimes be 100% higher than the cost of the original products (e.g., Chlorothiazide [Diuril], indomethacin [Indocin], mechlorethamine [Mustargen], and dactinomycin [Cosmegen]).3

The use of gray market suppliers also increases acquisition costs during drug shortages. A study conducted by Premier Inc. in August of 2011 recorded 1,745 gray market offers to providers, with an average markup of 650 percent.4 Many items, including those used in the treatment of critically ill patients, had markups even higher.



Adapted from Premier Gray Market analysis[4]

Drug shortages may force institutions to use higher-cost medications. For example, a hospital may have to purchase brand name Unasyn when generic ampicillin sulbactam is unavailable, or purchase branded oncology drugs such as levoleucovorin (Fusilev) during a leucovorin shortage.

Even more alarming, shortages of certain intravenous medications may jeopardize surgeries, interrupt cancer treatment and other medical procedures. Beyond the life-threatening impact that these situations can have on patients, they also mean lost revenue for hospitals that serve their communities.

Additionally, after a drug shortage ends, hospitals may experience a large surplus of the previously-scarce drug, resulting in higher inventory costs. During a shortage, hospitals often continue to order a product through wholesalers or manufacturers to fulfill contractual "failure to supply" clauses or to have a standing order on hand when the medication is available. When the medication shortage is over, suppliers sometimes fill backorders and standing orders, resulting in excessive supply and additional resources spent managing this new inventory. Lancaster

General Health has experienced this situation after resolution of backorders in vancomycin injection, dextrose 50% prefilled syringes, and phenylephrine, resulting in over a year's supply of medication on hand which in some instances was not returnable.

Finally, drug shortages often cause hospitals to rely on alternate suppliers which charge extremely high prices for critical medications. In each instance, Lancaster General Health first exhausted all other supply options and then evaluated the credibility of the alternate market supplier before resorting to this high-cost solution. Examples of alternate market supplier medication prices, compared to normal wholesaler acquisition prices, appear below:

Medication	Wholesale Acquisition Cost (WAC)	Alternate Supplier Pricing
Aminocaproic Acid 250mg/mL 25 x 20mL	$ 17.13	$ 375.00
Cisplatin 100mg Vial	$ 17.23	$ 120.00
Diltiazem 25mg/5mL SDV x 10	$ 11.58	$ 129.00
Hydralazine 20mg/mL 10 x 1 mL	$ 114.62	$ 295.00
L-Cysteine 50mg/mL SDV x 5	$ 60.30	$ 355.00
MultiTrace - 5 Concentrate 25 x 10mL	$ 78.39	$ 425.00
Paclitaxel 300mg/50mL Vial	$ 52.78	$ 695.00
Potassium Phosphate 4.4meq 25 x 50mL	$ 55.48	$ 325.00
Sodium Acetate 2meq 25 x 50mL	$ 57.89	$ 235.00
Valproate 500mg/5mL 10 x 5mL	$ 64.60	$ 275.00

Personnel

Drug shortages place a heavy logistical and administrative burden on hospitals. To combat these shortages, hospitals such as Lancaster General Health must reallocate existing staff to acquire medications, manage inventory, administer rapid changes to information systems, communicate to clinical staff, and develop alternative measures. Personnel may spend minutes to hours managing shortages, depending on the nature of the shortage.

Dealing with a drug shortage may require the work of a full range of providers, including pharmacy managers, technicians, front-line pharmacists, informatics and clinical pharmacists, pharmacy buyers, nurses, and physicians.

- **Pharmacy managers and supervisors:** daily review of current shortages, communication with front-line and clinical staff, patient/medication management determinations, development of alternative treatment strategies.
- **Pharmacy technicians**: management of inventory, including reallocation of supply to areas of need and monitoring of current supply.
- **Front-line pharmacists:** One-on-one communications with providers in acute situations who may not realize the shortage, ensuring an alternative therapy is available when needed, often with only a few minute notice (ex. OR).
- **Informatics pharmacist**: making necessary changes in information systems to accommodate alternative products or patient treatment strategies.
- **Clinical pharmacists:** development/implementation of alternative patient management strategies and patient education.
- **Pharmacy buyer** or **pharmacy purchasing department liaison:** daily review of current shortages, communication of shortage(s), researching strategy to manage including establishment of direct

order/allocation arrangements, bulk buying opportunities, compounding pharmacy opportunities, or gray market acquisitions.

- **Nursing**: patient education and implementation of alternative strategies.
- **Physicians**: decision making with regard to patient management and alternative treatments.

Patient Care / Safety

- Over the past year, medication shortages have resulted in delayed treatment, changes in therapy, and the omission of certain medications for many patients.

  Some examples affecting Lancaster General Health include:

  Bleomycin – This drug is critical to curative therapies for Hodgkin's lymphoma (ABVD regimen) and testicular cancer (BEP regimen), especially for young adult patients with curative diseases and good performance status. We receive medication via an allocation program by the manufacturer, which increases paperwork and *results in delayed initiation of treatment as well as rescheduling of patient appointments*. Alternative regimens are more toxic and impair fertility in young patients.

  Leucovorin – Due to a shortage of this drug within the past year, *for about two months, this drug was either omitted from regimens or patients were moved to alternative regimens that were potentially less effective or not well-tolerated*. The biggest concern with regard to this drug is the unknown and potentially negative effect on patients with colorectal cancer who receive curative/adjuvant therapy through Oxaliplatin and Irinotecan + fluorouracil based regimens. This drug has a synergistic effect with fluorouracil and increases the cancer-fighting ability of the fluorouracil.

  Doxil (Liposomal Based Doxorubicin) – Lancaster General Health experienced a shortage of this drug due to manufacturing issues. The manufacturer also established an allocation program (Doxil C.A.R.E.S) to assist in supplying medication to patients currently in need. Due to difficulties that Lancaster General Health has experienced in enrolling patients in this program, *we are currently experiencing patient treatment delays. Since the allocation supply has been available, we have had one patient accepted and at least 10 more waitlisted indefinitely.* Substitute treatment medications/regimens which have been required to be used in some cases run a higher risk of toxicity (including cardiac and/or hematologic events).

  Taxol (paclitaxel) – This drug is effective in the treatment of numerous cancers, including breast cancer, ovarian cancer, lung cancer, and gastric cancer. While shortages have not caused us to withhold care, other physician offices in our community have been unable to obtain this medication. Few affordable alternatives exist, because many providers use this drug as an alternative therapy in place of other medications that are currently on back-order.

  Fluorouracil – This drug is standard in numerous treatment regimens, the largest group being FOLFOX and FOLFIRI for colorectal cancer. While Lancaster General Health has not yet experienced a shortage of this drug to the point of withholding care, other provider offices in our community have, as well as subsequent home infusion services.

  L-Cysteine – This non-essential amino acid, which improves the solubility of calcium and phosphorus, is in short supply due to manufacturing issues. *Presently, we are unable to obtain this ingredient from any source, forcing us to omit it from patient regimens.* Intravenous nutrition supplementation is often necessary in pre-mature infants due to inadequate nutrient stores. Without L-Cysteine, providers must monitor the solubility of calcium and phosphorus in patients in order to ensure their safety.

Prochlorperazine – This injection, which is used for the treatment of nausea and vomiting, is presently unavailable. Prochlorperazine is a safer alternative to promethazine injections in patients with contraindications to several different medications.

Electrolytes, including injectable calcium gluconate and magnesium sulfate, are presently in short supply and increasingly difficult to obtain from any supplier. Providers use electrolytes in situations where urgent supplementation is necessary, to treat conditions or side effects from other medications, and in customized intravenous nutrition formulas. *The limited availability of electrolytes has resulted in rationing/restricting utilization and the use of higher-cost premixed intravenous nutrition formulas. Higher-cost alternatives carry potential safety concerns.*

Protamine is the reversal agent for heparin and is imperative in surgical and procedural settings. While Lancaster General Health has not yet had to deny the use of this agent to patients, our supply levels have been down to having only a few days supply in inventory. A lack of protamine at Lancaster General Health would threaten the scheduling of important surgeries and other procedures.

Additional examples that previously affected Lancaster General Hospital:

Epinephrine is an essential cardiac medication used in emergency code blue situations. We were unable to obtain the standard concentration of 1:10,000 1 mg/10 ml pre-filled syringes, which is supplied as a universally recognized single-use package in our emergency code carts. Our inability to obtain any product forced us to substitute epinephrine with a different concentration, 1 ml of the 1:1000 (1mg/ml) ampules (note: 10x greater concentration). The potential for medication errors was high, given that only 1 mL was required instead of 10 mL in these high-stress circumstances.

Propofol is a sedative and anesthetic agent with many advantages, including fast onset, short half-life once infusion is discontinued, and predictable clinical affects reached critical lows. The use of pre-filled syringes avoids waste. We required obtainment of Fresenius propofol, an alternative manufactured in the United Kingdom. The package insert cautioned against the use of this agent in individuals with soy or milk allergies, which is not a concern with the product we typically stock. Since many children and adults have milk or soy allergies, this represented a major safety concern.

Succinylcholine and Vecuronium are neuromuscular blocking agents that anesthesia providers use to induce and maintain anesthesia. Succinylcholine is particularly advantageous as a short-acting paralytic, a first-line choice for many surgical interventions. The shortage of succinylcholine led to our anesthesia department developing specific criteria and restricting the use of this agent. This resulted in the substitution of a longer-acting paralytic agent in place of this drug of choice for many operating room cases, which increased the risk for respiratory compromise due to prolonged paralysis. We were close to cancelling surgical procedures because of these risks, and surgeons threatened to cancel cases due to lack of availability of these agents.

Neostigmine was also in critical supply, which is required to reverse the effects of paralytic agents at the conclusion of a surgical intervention, which led to much anxiety in our anesthesia group.

Dexamethasone is most potent intravenous steroid specifically utilized for certain conditions. We were forced to stock a 10 mg/ml concentration of this drug, due to our inability to obtain any of our standard 4 mg/ml concentration. The potential for medication errors from the same total volume (1ml) were high.

Other concerns include:

- Utilization of gray market suppliers is concerning, as these are unofficial, unauthorized, or unintended suppliers of manufactured items. It is not always possible to obtain medication pedigrees to be certain of where the supplier obtained the medication from, or that it is not a counterfeit item.
- There is potential that substitution of similar medications if available may lead to medication errors or adverse events, especially if the prescriber is unfamiliar with the alternative's dosing or drug interactions.
- Medication shortages in procedural areas have the potential to cause delays in procedures and surgeries.

These logistical tasks consume significant dedicated hours from multiple stakeholders and staff working collaboratively on detailed plans to maintain safety, while requiring execution in limited timeframes.

During the past year, these collaborative discussions have included me personally, clinical pharmacy staff, nurses, and countless other caregivers working with:

- anesthesiologists and emergency physicians in contemplating how to maintain the airway of a patient presenting to the trauma center without the availability of a paralyzing agent;
- neonatologists considering how to best provide nutritional care to compromised premature infants;
- infectious disease specialists searching for alternative anti-infectives;
- oncologists discussing alternative treatment regimens midway through a course of therapy; and
- most significantly, how providers will explain to patients that we may not have the medication necessary to treat their disease.

I'd like to share a story relayed to me from our medical director of oncology concerning an 80 year old lady being treated for metastatic lung cancer. She was treated for three months with no side effects and in complete remission. One year later, her cancer returned and repeat treatment was planned, consented, and ordered. The drug was not available and an alternative was selected. The patient, who does not drive, needed to return so that we could re-consent, re-order and re-schedule treatment using an alternate agent. The patient subsequently suffered severe side effects, leading to the discontinuation of treatment until she recovers.

In our opinion, drug shortages are a national healthcare crisis.

Recommendations

Relieving and minimizing avoidable drug shortages requires both short-term interventions and longer-term, permanent solutions. We believe multiple opportunities exist and suggest the following actions:

First, we recommend the bipartisan legislation currently in both houses of Congress that requires drug manufacturers to report potential or existing production problems to the FDA. This key communication requirement would allow for appropriate planning and mitigation strategies to facilitate early identification, resolution and prevention of drug shortages. We believe this legislation will create greater collaboration and transparency between drug manufacturers and the FDA, which would facilitate more proactive approaches to avoiding critical situations.

Next, we recommend further collaborative requirements between the FDA and manufacturers to establish evidence-based allocation plans for critical drug therapies. Executed carefully, these actions could secure the pharmaceutical supply chain and direct available supplies to our most critical patient populations, making certain a drug is available in situations without reasonable alternatives.

Finally, we would encourage an exploration of incentive programs to encourage drug manufacturers to stay in, re-enter or initially enter the market, specific to critical drugs in short supply. These incentives could include creation of a fast track for approval of ANDA's, unapproved drugs, new production lines, alternate manufacturing sites or new suppliers of raw materials for drugs vulnerable to shortage, without compromising quality and safety.

Closing

Again, I want to thank the Committee for holding this hearing. Lancaster General Health offers its continued support and commitment to assist in the development of solutions that will help to prevent and mitigate risks caused by drug shortages. Thank you.

I will close with a statement made by Dr. Jacqueline Evans, from Cancer Care for Women:

> *"The entire oncology community, as a whole, has been kept in the dark as to the exact causes for the shortages of these medications...our patients and their families are the ones suffering. Their diseases are progressing, and they are actively dying, while we wait for the medications that could save their lives."*

Thank you.

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4. http://www.premierinc.com/about/news/11-aug/Gray-Market/Gray-Market-Analysis-08152011.pdf Accessed 9/15/11

Mr. PITTS. The chair thanks the gentleman.

Dr. DiPaola, you are recognized for 5 minutes for your statement.

STATEMENT OF ROBERT S. DIPAOLA

Mr. DIPAOLA. Thank you. Good afternoon, Chairman Pitts and Ranking Member Pallone and members of the subcommittee. My name is Dr. Robert DiPaola. I am director of the Cancer Institute of New Jersey, the State of New Jersey's National Cancer Institute-designated Comprehensive Cancer Center. I also speak as a member of the American Association for Cancer Research (AACR) and its Science Policy and Legislative Affairs Committee. Thank you for convening this hearing and recognizing the impact that the current drug shortage problem is having on our patients and on our ability to advance cancer research and improve patient outcomes.

You have heard about the effects of drug shortages on treating patients. As the director of an NCI-designated Comprehensive Cancer Center and a medical oncologist myself who treats and cares for patients, I have the same frustrations regarding the care of our patients and the negative impact of drug shortages. This impact is not only immediate for the patients in our clinics today, but also affects the future care of cancer patients because the next generation of cancer therapy is driven by today's clinical trials that are critical to meeting the national goal of improving the outcomes for cancer patients. Shortages of drugs is actually—as you know and you heard today—a very complex problem.

There are a number of ideas regarding what is causing them, and how they can be remedied. I am here today to discuss how this growing problem of shortages of already approved drugs, which in some cases, as you have heard, have been used and made for decades, is affecting our best cancer care, our clinical trials, and is threatening our ability to continue on our trajectory of steadily improving cancer patient outcomes.

FDA statistics show that the number of drug shortages has more than tripled over the past 6 years, with a marked increase in drugs involving sterile injectables, which negatively impacts the treatment of cancer patients—again as you have heard—that most shortages in oncology are sterile injectables. The medications in short supply include cancer treatment drugs, anesthetics, antimicrobials, and pain medications. A list maintained by the American Society of Health-System Pharmacists recently identified 193 shortages in 2011, of which 22 are cancer drugs, and the shortage is predicted to worsen. These include drugs that are the standard treatment regimens used to treat patients with many different cancers in adults and in children.

These shortages are now affecting clinical trial options for patients with cancer. Due to the uncertainty of being able to obtain many of these drugs, enrollment of patients on clinical trials has been delayed or stopped in several of our trials. Many of these drugs that are in short supply are a part of the standard regimens in which new treatments are added or compared to within a clinical trial. Many of the drugs on the shortage list are also used in our large national cooperative group trials. The Coalition of Cancer Cooperative Groups reports that approximately 50 percent of active cooperative group cancer clinical trials involve drugs subject to

shortages. Many reports contain examples in which sites are unable to enroll patients on approved clinical trials due to a lack of drug supply. Investigators in these clinical studies are unable to enroll new patients when the drug supply is not available; patients on-study are sometimes receiving alternate drugs when supply is not available, and there is concern about interpretation of results when drug substitutions occur.

It is important to remember that the impact from the drug shortages on clinical trials today will also have a long-term effect on cancer research and future treatment options for cancer patients. Clinical trials represent the final step of a long process of developing new therapies that improve the outcome of patients and add treatments for patients in which there were no effective prior options.

When, after years of effort, a single researcher discovers a potential new drug or treatment, that particular new drug is often best added to an existing treatment in combination and/or tested in comparison to the best current treatment in a clinical trial. If that trial yields positive results, patients can ultimately have access to a new and improved drug or treatment combination. Currently, however, we are running out of many of the existing drugs. When a clinical trial runs out of a drug, even temporarily, the trial results may be compromised, and an enormous amount of work and expense is wasted. This means that during a clinical trial, a shortage of only a few weeks in an existing drug might mean delays in years for developing a new drug. In other words, the drug shortages of today can have a ripple effect on the availability of new drugs and treatment combinations tomorrow.

Today, we estimate that 1 in 2 men and 1 in 3 women will develop cancer in their lifetimes. This year, over 1.5 million Americans are estimated to be diagnosed with cancer and more than half a million Americans are expected to die of their disease. That is more than 1,500 people a day or more than 1 per minute. While these numbers seem staggering, we have made great strides in our ability to diagnose, treat, and prevent cancer and are at a most promising time in cancer research.

Earlier this week the American Association for Cancer Research issued a progress report marking 40 years of progress in fighting cancer. In fact, thanks to advances made in cancer research, today more than 68 percent of adults are living 5 or more years, which increased from 50 percent in 1975. It was also reported that in the period from 1990 to 2007, death rates for cancer in the U.S. decreased by 22 percent for men and 14 percent for women.

The challenge we now face is to continue to turn groundbreaking science into lifesaving care at even greater speed. By facilitating clinical trials, we lay the groundwork for discoveries in basic cancer research to be translated into cutting-edge treatments for cancer patients.

The current drug shortage is hindering our ability to treat cancer patients overall. We are entering a new era of cancer treatment and prevention. However, an inability to have best treatment for our patients in general and conduct clinical trials is a serious impediment to our goal and will hamper our ability to reduce the toll of cancer for the people of our Nation.

Thank you.
[The prepared statement of Mr. DiPaola follows:]

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ROBERT WOOD JOHNSON
MEDICAL SCHOOL
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Testimony before the House Committee on Energy and Commerce Subcommittee on Health – September 23, 2011
Robert S. DiPaola, MD
Director, The Cancer Institute of New Jersey

Good morning Mr. Chairman and Members of the Subcommittee. My name is Dr. Robert DiPaola, and I am the Director of The Cancer Institute of New Jersey (CINJ), the State of New Jersey's only National Cancer Institute (NCI)-designated Comprehensive Cancer Center. I am also a member of the American Association for Cancer Research (AACR) and its Science Policy and Legislative Affairs Committee. Thank you for convening this hearing and recognizing the impact that the current drug shortage problem is having on our patients, and on our ability to advance cancer research and improve patient outcomes.

You have heard about the effects of drug shortages on treating patients. As the director of an NCI-designated Comprehensive Cancer Center, I have the same frustrations regarding the care to our patients and the negative impact of drug shortages. Unfortunately, this impact is not only immediate for the patients in our clinics today, but also affects the future care of cancer patients. The next generation of cancer therapy is driven by today's clinical trials that are critical to meeting the national goal of improving the outcomes for cancer patients. Shortages of existing drugs is a complex problem. There are a number of ideas regarding what is causing them, and how they can be remedied; I am here today to discuss how this growing problem of shortages of already approved drugs, which in some cases have been used and made for decades, is affecting our best cancer care, our clinical trials, and is threatening our ability to continue on our trajectory of steadily improving cancer patient outcomes.

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It is important to remember that the impact from the drug shortage on clinical trials today will also have long-term effects on cancer research and future treatment options for cancer patients. Clinical trials represent the final step of a long process of developing new therapies that improve the outcome of patients, and add treatments for patients in which there were no effective prior options. When, after years of effort, a researcher discovers a potential new drug or treatment, that new drug is often best added to an existing treatment in combination and/or tested in comparison to the best current treatment in a clinical trial. If that trial yields positive results, patients can ultimately have access to a new and improved drug or treatment combination. Currently, however, we are running out of many of the existing drugs. When a clinical trial runs out of a drug, even temporarily, the trial results may be compromised, and an enormous amount of work and expense is wasted. This means that during a clinical trial, a shortage of only a few weeks in an existing drug might mean delays of years for the development of a new drug. **In other words, the drug shortages of today can have a ripple effect on the availability of new drugs and treatment combinations tomorrow.**

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The challenge we now face is to continue to turn groundbreaking science into lifesaving care, at an even greater speed. By facilitating clinical trials, we lay the groundwork for discoveries in basic cancer research to be translated into cutting-edge treatments for cancer patients. The current drug shortage is hindering our ability to treat cancer patients. We are entering a new era of cancer treatment and prevention; however, an inability to conduct clinical trials is a serious impediment to our goal and will hamper our ability to reduce the toll of cancer on the people and economy of our nation.

Thank you.

Mr. PITTS. The chair thanks the gentleman and thanks all of our 7 witnesses for your thoughtful testimony. And we will begin questioning at this time. I recognize myself for 5 minutes for that purpose. Let me begin with you, Mr. Paoletti. A couple of questions. Can you walk us through what happens from your perspective when there is a drug shortage? Who notifies you? How much warning do you get? What do you need to do to notify the people in your organization?

Mr. PAOLETTI. It differs in every instance, but like I said, a lot of times we find out when a drug order doesn't come or our buyer-and-receiving process, through the receiving process, we learn that we didn't get a medication on order. The buyer then has to follow up with the wholesaler to find out if that is a temporary outage, when we would maybe next expect that, and then that would relay into an investigation of more than probably for us 100 to 150 inventory locations in automated cabinets throughout our facility. So we look at what we have on hand, how much we continually use on a day-to-day basis, and estimate how much supply we would have if we continued business as is.

Based on that and the information we get, we have to convene a team. It is typically pharmacists, nurses, the specific stakeholder physicians depending on what medicinal it is. We look at the indications, we look for alternative therapies that we may have available to us, and kind of assess how critical the nature of the shortage is. And then based on that, we have to create action plans. Sometimes it involves the pharmacy manually preparing specific minimal doses of medications to make our supply last as long as conceivably possible. That was the case with one instance last October that to me was the tipping point of the drug shortages with a drug called succinylcholine. We came down to the last couple days of therapy and really contemplating cancelling surgeries and, you know, how we would, you know, manage those situations.

Mr. PITTS. Is there any way, at present, for you to anticipate a shortage?

Mr. PAOLETTI. Through some online web sources, as good as the information is based on what the drug companies reveal and what is published, we have an active surveillance program now that goes out to the FDA Web site, that goes out to ASHP resources to look at that information, which sometimes is published with alternatives. So the University of Utah's Drug Information Center has been very helpful in that regard, but it is only as good as the information that is available. And a lot of times, no information exists until we self-report that we are having difficulty.

Mr. PITTS. Thank you. Let us just go down the line. Mr. Kafer, from your company's experience, what are the main reasons for a drug going into shortage, and how does your company work with FDA to notify them of the shortage?

Mr. KAFER. From a notification standpoint, our primary point of contact when we become aware of a shortage for any number of reasons we could have had a manufacturer lot rejected during release testing. And what that means is after you finish your manufacturing process, every injectable goes through about a 3- to 4-week series of tests. If those tests fail for quality reasons or not meeting a specification, you reject that lot. If we anticipate a short-

age, our primary point of contact continues to be FDA drug shortage. As testified this morning by Dr. Kweder, I think the point was made that they do not immediately post that information because that can trigger additional behavior where the awareness of the potential shortage could lead to purchasing of another generic product or even another comparative therapy which can drain those supplies as well. So we coordinate directly with the drug shortage group and then we coordinate with our hospital partners and our distribution partners.

Mr. PITTS. And how have you worked with the FDA to alleviate a shortage?

Mr. KAFER. We have worked extremely well with the FDA. There has been many instances in which we have collaborated. I think through the drug shortage group, they have been playing quarterback on this. I think we mentioned earlier this morning, it is not a formal process, but they do a fantastic job in pulling instances together. There has been at least 3 occasions where we had submitted a prior approval supplement, and by definition of that, that is an extensive review that indicates that we have had significant changes to a product or process which would typically take long, but they have been able to expedite those reviews and get those approved in about a 3-month period that allowed us to get those critical products to market.

Mr. PITTS. Thank you. Mr. Gray, can inventory management practices create the impression of a drug shortage, and how do distributors and others work to avoid that situation?

Mr. GRAY. Well, inventory management practices or just-in-time or whatever you want to call it, those are actually across the supply chain from just-in-time production to just-in-time delivery. Our members focus on the delivery side, the manufacturers on the production side. And that actually is a process developed over the last 25 years in the consumer goods area, which is really to spread out the predictability of manufacturing, as well as altering both the manufacturer, the wholesaler, and the retailer or pharmacy when product potentially is short. It is more real-time information across. So the reality is the inventory management programs are really there to spot the shortages potentially before they happen, and that is really what has been developing since the late 1980s from the food industry into the pharmaceutical industry.

So I am not sure there is a connection there. I have heard that today. If you really look at the science of that, the mentality behind those is really to identify those shortages early on.

Mr. PITTS. Now, when a secondary distributor purchases a drug product, they often pay more than the primary distributor would pay. So if they then charge more for the drug, they are simply responding to market, aren't they? This is not a gray market practice, is it? Can you contrast that with the gray market?

Mr. GRAY. I can't speak to the secondaries. I know our members, our 34 primary wholesalers, we are buying directly from manufacturers, and then we sell only to state-licensed entities, be that a secondary distributor, a hospital, pharmacy, or whatever. And so, usually, we are under contract pricing with the manufacturers for those products. So if we are selling them on down to a provider, it is usually a contract price already preset. What a secondary

would do with that product, I do not know. In terms of pricing, I have no information on that.

Mr. PITTS. Thank you. Mr. Colgan, in your testimony, you state that there is no one solution to this problem; however, you stress the importance of enacting legislation to require manufacturers to notify FDA of possible shortages. Can you explain why this requires legislation to accomplish and why it needs to be done on a confidential basis?

Mr. COLGAN. Sure. I think when there is a leak or a hole in the dam, I think you need to stick your finger in it first to stop the leak, and then you need to explore what the reason is for it, and then you need to solve the problem. What this legislation really does is sticks your finger in the hole in the dam to stop the leak. And basically, we have heard from testimony today from the FDA that they have been able to basically abort 99 drug shortages this year with regards to early warning systems. So we believe that is needed.

I am definitely not in favor of regulation when regulation isn't needed, but honestly, anything that I am putting in my body or my mouth, I want to make sure that it is manufactured in the right way, that it is done correctly. And certainly, we support the FDA in terms of their role in protecting drug safety within this country. Needless to say, they need to be able to have the power and the jurisdiction to enforce early reporting of drug shortages.

And the other thing that I said I think was really most important is get the word out to everybody at the same time. It is beyond me sometimes that others have drug product when I don't have drug product. When drugs come back onto market, there are only certain places that you can get those drugs from and you can't get it from your normal supply chain. So again, I think we need regulation in order to solve the problems that we have at hand.

Mr. PITTS. Thank you. Mr. Alkire, we have heard that often the end users of drugs that go into shortage have very little advanced warning. For example, a surgeon may find out that the preferred anesthetic drug is not available only after the patient is prepped and on the operating room table. How does this happen? How do hospitals give warning of shortages to their own doctors?

Mr. ALKIRE. For the most part, now, I have not necessarily heard that, but for the most part, there is very strong communication that actually occurs in the hospitals and doctors are made aware of what is happening from a shortage, especially as they are doing prep for these procedures. And then they have to go about figuring out what are the potential clinical alternatives to ensure that their patients are getting the highest quality care.

Mr. PITTS. OK. Dr. Penley, how many drugs that you use in your practice regularly go into shortage? It appears that there are a finite number of drugs that regularly go into shortage.

Mr. PENLEY. The current number for oncology drugs is around 23 I believe, and those are very commonly used agents. So we would use most of them in our practice on a day-in, day-out basis.

Mr. PITTS. And is there any way, at present, for you to anticipate a shortage?

Mr. PENLEY. On a practice level, it is difficult. We get information the same way most of these folks do, through the FDA Web

site or the hospital pharmacist Web site. ASCO, our national organization, serves primarily as an information-gathering and distributing service there for our members, and certainly at times when we see that they are going to be prolonged shortages, ASCO convenes expert panels to try to brainstorm and come up with the best available work-arounds in situations where we have to make substitutions. We try to bring together the best minds in oncology so that they can come up with workable and reasonable solutions for our patients when we know that those drugs are going to be in shortage for any length of time.

Mr. PITTS. Thank you. Dr. DiPaola, your description of the impact of drug shortages on future cancer patients because clinical trials may have to be stopped or not started in the first place is quite compelling. You mention that 50 percent of the cooperative group trials involve drugs that are subject to shortage. That sounds like it should have a devastating effect on cancer research. Could you give us an idea of the magnitude of this problem?

Mr. DIPAOLA. I think that it is, you know, as we are all concerned with, you know, the shortage even worsening and already we are seeing a number of trials even with our cancer center as an NCI-designated Comprehensive Cancer Center, we take care of patients with both the best standard treatments and then offer clinical trials for patients who want that option. And those clinical trials are geared towards our new discoveries of new regimens. If a clinical trial is compromised because it needed to substitute a particular drug for another drug or, in some cases, clinical trials won't allow a substitution, all of the work that went into the discovery getting to the point of the clinical trial is going to be compromised.

And so, you know, we have made gains on cancer research overall, but ultimately, the discoveries in terms of the targets in the lab, the drug development, and then either the comparison to these existing drugs or the addition of these new targeted agents to existing drugs make it very, very difficult to continue this. And I agree, you know, those statistics relate to data we have been given regarding the cooperative group trials. Those are usually the large national trials that do comparisons. And nowadays, most of the trials don't contain a placebo, so at least the existing drug is part of the clinical trial. So this already is a very difficult and concerning problem, and the way the stats are looking, may worsen.

Mr. PITTS. Thank you. I have gone way over my time. I thank the ranking member for his indulgence and I will yield to Mr. Pallone for such time as he may consume.

Mr. PALLONE. Thank you, Mr. Chairman. Let me ask unanimous consent to put in the record this statement from I guess the Fight Colorectal Cancer group on the U.S. drug shortage. You have it.

Mr. PITTS. Without objection, so ordered.

[The information follows:]

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Fight Colorectal Cancer Statement on the U.S. Drug Shortage

September 23, 2011

There are severe shortages of more than 100 life-saving drugs in the United States – several of which are key to treatments for colorectal cancer patients: leucovorin, fluorouracil (5-FU), and irinotecan. Over the past 10 years, rolling drug shortages are becoming more frequent and likely will worsen.

There *is* a substitute for leucovorin. A significantly more expensive new brand-name drug, *Fusilev*, has been added to national care guidelines, which should facilitate coverage, at least in part, by Medicare and private insurers. National guidelines also suggest use of lower doses of leucovorin, or, as a last resort, treatment without leucovorin can be considered when combined with a possible increase in 5-FU dosage. However, 5-FU is now also in short supply.

"For patients living with colon and rectal cancer, this is a crisis. We have spoken with a patient with late stage rectal cancer in California who was unable to be treated for his cancer because of the 5-FU shortage," said Carlea Bauman, president of Fight Colorectal Cancer. "Another patient with curative disease was unable to get his recommended treatment because of the leucovorin shortage. And publicly-funded clinical trials are being suspended due to the shortages."

A recent report from the Institute for Safe Medication Practices (ISMP) has uncovered a frightening number of near misses, patient harms and actual errors due to the drug shortages. It states that:

- One out of three reviewed facilities had a serious error that was caught in time — a near miss
- One out of four had an actual medication error resulting from the shortages
- One out of five reported actual adverse outcomes for patients

The September 23, 2010 issue of the ISMP Medication Safety Alert reported that survey respondents were alarmed by the:

- Increasing numbers of critically necessary medications in short supply
- Need to use unfamiliar alternative drugs — which are often more expensive
- Potential for mistakes and patient adverse events associated with alternative drugs or doses
- Lack of advance warning about impending shortages
- Time lost due to the management drug shortages

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How can there be shortages of long-used, life-saving medicines in the United States? A summit of manufacturers, oncologists, purchasers and regulatory officials held in November 2010 revealed – not surprisingly – that there's no single reason or solution.

First, even generic injectable drugs are complicated and have long production time. Second, more than 80 percent of their ingredients come from outside the United States. Third, pharmaceutical company consolidations are often resulting in only one or two manufacturers for key drugs. If one of just two manufacturers has production problems or a disrupted international supply-chain of ingredients, that instantly creates a 50 percent shortage – which hits quickest in community and rural oncology practices that typically order small amounts of any one drug.

Finally, there is a lower profit margin in generics, as pharmaceutical companies race to make the new brand-name targeted therapies.

"If companies aren't going to make money off these vital generic drugs, then they aren't going to produce them," said Bauman. "In that case, the Food and Drug Administration needs to allow importation; otherwise, patients won't get the generic drugs they need, or will be forced to use much more expensive brand-name drugs."

Fight Colorectal Cancer supports legislation introduced by Rep. Diana DeGette (D-CO) and Sens. Amy Klobuchar (D-MN) and Bob Casey (D-PA) that would put in place "early warning" systems, requiring manufacturers to notify the Food and Drug Administration (FDA) of any manufacturing or supply problems that could cause a drug shortage.

Longer-term fixes, which Fight Colorectal Cancer will continue to push for, include streamlining FDA procedures to allow importation of crucial drugs or quicker changes in ingredient sources; possible tax breaks to make vital lower-cost generic drugs more profitable; or even creating a national stockpile of vital drugs.

Mr. PALLONE. And I am going to just go back to what you said, Mr. Chairman, or follow up on what you asked Dr. DiPaola, who, as you know, is from my district. The Cancer Institute is in New Brunswick in my district.

Do you have an example of a clinical trial that was halted at the Cancer Institute because of the drug shortage? Is there an actual example at the Cancer Institute of New Jersey where you had to halt because of the drug shortage?

Mr. DIPAOLA. Yes. I mean there are actually a number of examples, trials that we were about to launch that we have made, you know, the plans and development to start a clinical trial. Most of them, Congressman Pallone, have to do with trials where a new drug is added to existing therapies. And we have had difficulties in at least 1 or 2 trials where a new drug was added to a combination that included TAXOL as one particular example. And the trial was held in terms of initiating the trial. What ends up happening is is in the clinic, we then have concern in offering patients who actually come to the center looking for these new options in terms of clinical trials, the trial when we are not assured of the, you know, particular drug supply.

There was another trial where a young patient with breast cancer was enrolled where Doxil was included, along with another set of combination of drugs, and it required amendment to the trial to allow the patient to be treated, to change the drug from Doxil to another agent, which again has concerns about compromising the trial, and again the delay involved in trying to look at options and then even change the drug because in that case the trial allowed.

And then in a number of cases, delayed trials where doxorubicin was part of the regimen, again with a novel what is called PARP inhibitor, which in the case I am referring to is an NCI trial that was delayed. So all of these, you know, taken together, any one of these, you know, weeks, months delays really delay us getting an answer. And more importantly, patients are coming because they are concerned that in that case, the standard option may not be what they are looking for enough and they are looking for these options in clinical trials.

Mr. PALLONE. Sure. I mean just give me an idea. I mean how do you think the drug shortage impacts the future of cancer research and treatment? I mean are you concerned and, you know, just in an overall sense?

Mr. DIPAOLA. Well, I mean I think, you know, it is going to be important and that is why I think it is important that everybody get together in a collaborative way to look at all of the root causes and come up with solutions because it is concerning, especially if it does worsen. And, at least as statistics would indicate ,that it is. So I think it is concerning. I think that we need to keep pushing forward in all areas of research. I mean as you know well, you know, it includes the discovery on the basic science end leading into the efforts of translating into clinical trials. But it is concerning, especially with the statistics that we are seeing.

Mr. PALLONE. OK, thank you.

I wanted to ask Mr. Kafer from Teva a couple things. A frequent cited reason for shortages is manufacturing problems, and of course we have heard that sterile injectable drugs are hard to manufac-

ture. So if your supplier, I guess, has a problem, that can lead to a shortage. So obviously, there are circumstances outside of your control that can interfere with your ability to deliver a product. I mean are these problems unique to the drugs prone to shortages? For example, are all sterile injectable drugs prone to shortage or is there something about these drugs that makes controlling their manufacture more difficult? Are there things manufacturers can do to avoid these problems?

Mr. KAFER. I think one of the things you need to understand from a complexity standpoint, by the nature of a sterile manufacturing facility, it is sterile and it is a very complex manufacturing environment. Picture, if you will, people in spacesuits kind of doing the prep work. If you are in an oral solid manufacturing facility, it is much different. So there is more complexity.

The other thing within a manufacturing facility, each technology has its own defined manufacturing line or manufacturing suite. For instance, you cannot manufacture cytotoxic oncology products on the same line you would manage hormones or something of that nature. Many of the products, some of them are lyophilized, which is a powder that has a very unique manufacturing suite. And a liquid fill line is also a very unique manufacturing suite. So it is possible that within one manufacturing facility, you have a disruption in just one suite, one of those technologies. And one of the questions we have heard repeatedly from the panel is specific to oncology, and it is a very dynamic complex environment. And unfortunately, over the last couple of years, industry has had some disruptions within those manufacturing suites that we are in the stages of recovery so we are manufacturing product, but we are in a slow build and it is impacting, obviously, patients as the panel has testified today.

Mr. PALLONE. Of course, we always worry not only today but in so many cases about active ingredients in drugs sold in the United States that are supplied from abroad. So I guess I am, you know, asking you to what extent that is problem and, you know, in the wake of heparin, of course, there is major concern about cracking down on some of the ingredients that are sold abroad. I mean to what extent does the availability of these ingredients from abroad impact this discussion today? I mean it is very likely that, you know, we put a lot more regulation and make it more difficult for things to come from abroad.

Mr. KAFER. Regardless if the materials coming from abroad or domestically, to your point regarding the heparin scare of years ago, the testing requirements and scrutiny that we will go through before we will release the active ingredient into production is significant, and we will not jeopardize that. So the testing requirements that we impose on our manufacturing partners on the API side are significant. And there has been repeated instances in which we are failing API coming in for production because they have not met our specifications. If that does happen on a repeated basis, then you are obviously going to have a gap in readily available material to produce product. So without question for good reason that we are testing that material to the requirements that we are required to and we will not use it unless it passes those tests.

Mr. PALLONE. Now, you heard me earlier mention your testimony in the context that you and Dr. Kweder, I guess, acknowledged in your testimony that it can take 2 to 3 years for FDA to approve a new facility or API supplier, and obviously, that is not a good situation. However, on the first panel, they also said that FDA has the flexibility to adjust resources so that it can approve facilities and suppliers very quickly. I mean has that been your experience that that flexibility is exercised or works or are you sort of sticking to this 2 to 3 years?

Mr. KAFER. The standard process as it exists today historically has been 2 to 3 years for an API secondary manufacturer approval or a manufacturing site traditional past. And, you know, those reviews take time because it is a complex review and it does require extensive work. At the same time, yes, we have seen expedited reviews in that area. We have been the beneficiary of expedited reviews to handle critical situations.

But also in my earlier statement, in my opening remarks, I mentioned a lot of the shortages are unforeseen. We are applying a great deal of coordination and a great deal of collaboration when we are solving the problem. And as a standard of practice, is it possible to expedite some of those reviews as a standard of practice was the point of my written testimony. But we do see on a routine basis now where applicable, without jeopardizing the product, you know, we never jeopardize the product or system, but we have seen collaboration to expedite those reviews in a matter of months.

Mr. PALLONE. And I appreciate that, but I guess what I am trying to say is, you know, when I mentioned your 2 or 3 years in your written testimony, I don't want to put words in their mouth but it was sort of suggested at the first panel that maybe it is not so much a problem because we can use this flexibility, but I mean is it your experience that there is enough flexibility to deal with these situations or not? I mean I know that is a difficult question. You don't have to say——

Mr. KAFER. I have had experience where we have had expedited reviews, collaborative work, and favorable outcomes. You know, the volume of work that could be forthcoming based on continued remediation, I can't predict and I can't, you know, forecast that impact. But prior to significant shortages—which the industry planned for—I mean, so we would plan for a 2-year review, we knew what that type was, but at the time when we were just making sure we had redundancy in place for those critical products, it wasn't of immediate need. Now that we are seeing immediate need, we are seeing those expedited reviews.

Mr. PALLONE. All right. Thanks. I just wanted to ask one more question of Mr. Colgan here, Mr. Chairman.

In his written testimony he suggested a number of incentives that might be provided to encourage manufacturers to stay in the field or enter the field and, of course, I think in principle that incentives are a good idea. If we can get more companies to manufacture these products or to produce excess supply, you would think that shortages would be less likely to occur and less severe if they do occur. But that being said, the suggestions in your testimony I think need a little more fleshing out for me to better understand,

you know, what you are trying to achieve or how you would achieve the goal.

And I know they are only presented as options to be further explored, but I was puzzled by the suggestion of granting temporary exclusivity for a new product line of drug either already in short supply or deemed vulnerable to a shortage considering that the goal would seem to be to get as many companies into the field as possible. It would seem that granting exclusivity would appear to be doing the exact opposite, and it is my understanding that exclusivity works best as an incentive when the company is the only one manufacturing the product, or in the case of a new generic, is the only company offering a generic alternative to a name brand. So it is not clear to me that granting exclusivity would be much of an incentive. And I am not trying to be critical. I just wanted you to walk me through how you think this would actually work practically.

Mr. COLGAN. Well, there are 2 things here. One is the generic user fees and we believe those can be utilized to incent manufacturers to enter in the market or reenter into the market in producing a product that they have produced before or not produced. We have drugs that are single-source sometimes or we have drugs where we don't have enough production and throughput. In those situations, we think within limits this is a concept that needs to be explored in terms of some sort of temporary exclusivity in the market so that there is a period of time that would incent a manufacturer to get into the market and produce the product. It could be that the FDA provides accelerated review of a supplemental NDA to that manufacturer, allows that manufacturer a period of 6 months or so to put the product together and produce the product. We see the whole idea of incenting the industry to jump into the generic market as being really important.

Let me give you an example of that. Hopefully, that will play out and you will understand. Right now, we have production problems with carmustine and we use this in non-Hodgkin's lymphoma as a conditioning therapy in getting patients ready for autologous bone marrow transplants. Right now, that is not a medically necessary drug because we can use bendamustine. If I have a patient who is on carmustine, I would pay $938 for that patient's drug if they had a body surface area of 2. For bendamustine I would pay $14,440. It advantages us to have other manufacturers in producing carmustine so we have adequate supplies and some sort of incentive that would allow them to do that so we are not forced to use bendamustine would be very important to us in terms of securing a supply line for that drug. And it certainly adds up to the economics of the situation, too, in terms of being able to supply a drug that is category one, recognized as the appropriate treatment for the patient, but also provides the lowest overall cost continuum of providing the care to that patient.

Mr. PALLONE. All right. Thanks a lot. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and that concludes our round of questioning. Again, I would like to thank the witnesses for your testimony, for answering the questions. We will ask you to please respond to any questions in writing.

In conclusion, I would like to thank all the witnesses and members for participating in today's hearing and remind members that they have 10 business days to submit questions for the record, and then I ask the witnesses to please respond promptly to the questions. And members should submit their questions by the close of business on October 7.

There being no further business, the subcommittee is adjourned.

[Whereupon, at 2:18 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

Opening Statement of Energy and Commerce Committee
Chairman Fred Upton
Examining the Increase in Drug Shortages
Friday, September 23, 2011

Thank you for holding today's hearing on drug shortages. Since 2005, drug shortages in the United States have more than tripled. We are not talking about unimportant, unusual or prohibitively expensive drugs. These are drugs that are crucial to patients and the doctors who care for them.

These shortages very often affect the sickest patients, including children with cancer and patients in hospital intensive care units. Furthermore, these drugs are most often generics that have been used for many years and are extremely low cost. It is not that the drugs are unaffordable; they are just not available.

It is hard to imagine that, in the United States, a pediatric oncologist, faced with a child who has a potentially curable cancer, must choose a treatment plan for that child that may be less effective and may cause that child to suffer undesirable side effects because the preferred

drug is not available. This is a scenario that would be hard to accept in a third world country; it is simply intolerable in the best health care system in the world.

I want to thank the witnesses for appearing before the committee today. I think this hearing will serve as an excellent starting point to gather needed information about the various root causes of this critical problem and to explore possible solutions; so that, when facing a child with cancer, no doctor in this country has to say to that child and his or her parents: "I may not be able to cure you because the drug I need is not available."

I thank the Chairman for holding this hearing. I yield back the remainder of my time.

Statement from Representative John D. Dingell
House Committee on Energy and Commerce
Subcommittee on Health
"Examining the Increase in Drug Shortages"
September 23, 2011

I thank the Chairman for holding today's important hearing.

Over the last six years the number of drug shortages has nearly tripled, resulting in hospitals, pharmacies, providers and patients scrambling for the drugs they need.

The headlines of this summer speak volumes:

- *"Drug shortages threaten patient care."*
- *"Drug shortages set to reach record levels."*
- *"Shortage of key hospital drugs a 'major crisis'."*
- *"Drug prices soar as hospital suppliers are forced into 'Gray Market'," and,*
- *"Dangers of worsening drug shortages; remedy unavailability could start costing American lives."*

This is not an isolated problem. Shortages are affecting hospitals from Detroit to Nashville to Houston. In a survey by the American Hospital Association, three out of four hospitals reported rationing or restricting the drugs in short supply. More than 80 percent reported delaying treatment and nearly 70 percent had to substitute less effective treatments for their patients.

These numbers are astounding. For patients needing certain treatments they could be at risk of having their drugs rationed, restricted, or substituted for a less effective treatment. This is absolutely unacceptable, and Congress and the federal government cannot sit idly by and allow this problem to worsen.

We know that there are many different issues that can cause a drug shortage - availability of raw materials, the complexity of manufacturing certain treatments or sudden unexpected increases in demand. But at the end of the day the ultimate impact of these shortages is potentially deadly, causing patients to go without care or, even worse, turn to the gray market to purchase the life-saving drugs they need. An active, unregulated gray market has resulted in consumers, pharmacists and hospitals purchasing potentially ineffective, contaminated, counterfeit or adulterated products.

I hope that today's hearing will help the Committee and its Members to understand the problem at hand, learn about the causes of the problem, and help to explore ways that Congress, the Department of Health and Human Services and the Food and Drug Administration can make improvements to minimize the impacts drug shortages are having on patient care, and ensure the quality of drugs in our Nation's supply is not comprised.

Statement for the Record
Drug Shortages health subcommittee hearing
Representative Edolphus "Ed" Towns

Mr. Chairman and Ranking Member Pallone, thank you for holding this important hearing on the drug shortage issue. I am pleased that the committee is engaged in a bi-partisan discussion on this issue as it is so very important to all of our constituents.

Chronic and increasing drug shortages are becoming issues of grave concern because they have serious consequences for patient safety, quality of care and access to therapies. Drug shortages lead to delays in treatment and force the use of alternative drugs with which the provider may not be as familiar. Using unfamiliar alternative drugs can result in unintended harm to the patient through errors in dosing and administration, and in unexpected side effects.

Shortages also are costly to hospitals and health systems in terms of staff time and other resources to manage the shortages and the increased cost of buying alternative drugs "off contract." Critical sterile injectible drugs, mostly older generic drugs, accounted for the majority of drug shortages in 2010 and 2011. As reported by the American Hospital Association, these shortages often came with little or no advance notice from the manufacturers.

Drug shortages are complex, with many causes ranging from raw material sourcing, manufacturing problems (quality control and compliance issues), manufacturer consolidation and business decisions that result in drugs being discontinued. While there are some steps the FDA can take to mitigate or resolve drug shortages, the agency's current statutory authority in this area is limited.

In discussions that I have had with hospitals, I understand that they believe that there are many changes – in addition to the *Preserving Access to Life Saving Medications Act* (H.R. 2245) - that could be made to help to alleviate drug shortages. Other steps include removing obstacles so that the FDA is able to streamline approval of drugs in shortage. An example would be to develop a fast track for approval of new production lines, alternate manufacturing sites or new suppliers of raw materials for medically necessary drugs in shortage. Improved communication among stakeholders also would help. For example, more formal communication between the FDA's Drug Shortage Program, Office of Generic Drugs and the Office of Compliance could help to minimize unnecessary delays in resolving quality systems issues for shortage drugs. Further, hospitals in my district believe that Congress should explore establishing appropriate incentives for manufacturing redundancies or other means of producing emergency supplies as part of the FDA approval process for drugs that are deemed vulnerable to shortages. Also the rapidly escalating number of shortages and the threat that these shortages represent to patient safety require that the FDA have adequate resources and a sufficient number of experienced staff to manage drug shortages. Therefore, Congress should authorize and appropriate funding for FDA activities that prevent or mitigate drug shortages.

With drug shortages becoming increasingly frequent, surveys of hospital staff were conducted to assess how the shortages have impacted patient care. With 820 hospitals responding, almost 100

percent reported a shortage in the last six months and nearly half of the hospitals reported 21 or more drug shortages. More than 90 percent of hospitals reported shortages of surgery or anesthesia drugs and emergency care drugs, and two-thirds reported shortages of chemotherapy drugs.

While many hospitals were able to find alternative sources for the drugs in short supply, the survey revealed that in the past six months:

- Hospitals report that they have delayed treatment (82 percent) and more than half were not always able to provide the patient with the recommended treatment.
- Patients got a less effective drug (69 percent).
- Most hospitals rarely or never receive advance notification of drug shortages (77 percent) or are informed about the cause of the shortage (67 percent).
- The vast majority of all hospitals reported increased drug costs as a result of drug shortages.
- Most hospitals are purchasing more expensive alternative drugs from other sources.

I hope that hospitals, the FDA and other interested organizations will continue to work together to address the serious issue of drug shortages to ensure patient safety.